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Review article

Clinical effectiveness of pharmacological and non-pharmacological treatments for the management of anxiety in community dwelling people living with dementia: A systematic review and meta-analysis

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ABSTRACT

People living with dementia commonly experience anxiety, which is often challenging to manage. We investigated the effectiveness of treatments for the management of anxiety in this population. We conducted a systematic review and meta-analysis of randomised controlled trials, and searched EMBASE, CINAHL, MEDLINE and PsycInfo. We estimated standardised mean differences at follow-up between treatments relative to control groups and pooled these across studies using random-effects models where feasible. Thirty-one studies were identified. Meta-analysis demonstrated non-pharmacological interventions were effective in reducing anxiety in people living with dementia, compared to care as usual or active controls. Specifically, music therapy (SMD–1.92 (CI:−2.58,−1.25)), muscular approaches (SMD-0.65(CI:−1.02,−0.28)) and stimulating cognitive and physical activities (SMD–0.31(CI:−0.53,−0.09)). Pharmacological interventions with evidence of potential effectiveness included Ginkgo biloba, probiotics, olanzapine, loxapine and citalopram compared to placebo, olanzapine compared to bromazepam and buspirone and risperidone compared to haloperidol. Meta-analyses were not performed for pharmacological interventions due to studies' heterogeneity. This has practice implications when promoting the use of more non-pharmacological interventions to help reduce anxiety among people living with dementia.

1. Introduction

Dementia affects approximately 47 million people worldwide (Emmady and Tadi, 2022). In England, most people with the condition live at home (61%) and the others in care homes, with or without on-site nurses (Alzheimer's Research UK, 2022). They commonly experience distressing behavioural and psychological symptoms (BPSD), including anxiety (Zhao et al., 2022; Kuring et al., 2018). Systematic reviews have identified anxiety pooled prevalence rates of 14–39% in this population (Kuring et al., 2018; Zhao et al., 2022).

Despite its high prevalence, little is known about how adverse outcomes combine in people with dementia-related anxiety, although there is some evidence to suggest an association with further cognitive decline, reduced quality of life, agitation and depression (Seignourel et al., 2008). It is therefore important to manage anxiety in people living with dementia, to improve outcomes including quality of life (Banerjee et al., 2006). There is further evidence for people living with dementia who experience other common and sometimes related distressing symptoms, such as depression or agitation. Agitation is associated with increased medication use, falls, fractures, and infections (Fillit et al., 2021). There is also an increase in all-cause mortality, cardiovascular mortality (Georgakis et al., 2016), and worse outcomes following hip fractures (Bellelli et al., 2008) among people with both cognitive impairment and depression.

In practice, psychotropic medications are used often to reduce neuropsychiatric symptoms in dementia, including more severe

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anxieties (Watt et al., 2020), despite a lack of guideline recommendations for pharmacological interventions. There is limited evidence supporting such prescribing; studies rarely report adverse effects, some are poor quality, and results are mixed (Dudas et al., 2018). There is growing yet limited evidence investigating the effectiveness of pharmacological interventions for neuropsychiatric symptoms in people living with dementia in the community, such as antidepressant drugs, which are commonly prescribed for anxiety in the general population (Banerjee et al., 2011; An et al., 2017).

Current guidelines, for example in England, recommend psychological therapies to treat people with anxiety and dementia (NICE, 2018b) but it is unclear if conventional therapies, such as cognitive behavioural therapy (CBT), are effective in people with dementia due to limited evidence, that is mostly of low quality (Orgeta et al., 2015). A recent systematic review investigating pharmacological and non-pharmacological interventions in people living with dementia and depression found non-drug interventions were more effective than drug interventions for reducing depression symptoms when compared to usual care (Watt et al., 2021). These included: cognitive stimulation, cognitive stimulation combined with a cholinesterase inhibitor, massage and touch therapy, multidisciplinary care, occupational therapy, exercise combined with social interaction, and cognitive stimulation and reminiscence therapy. To our knowledge, a similar review has not been conducted investigating the effectiveness of treatments in the management of anxiety in people living with dementia. There are several Cochrane Reviews exploring specific intervention types, such as cognitive stimulation, in people living with dementia but these do not specifically focus on anxiety and only focus on one intervention type (Orgeta et al., 2022; Van Der Steen et al., 2018; Woods et al., 2023; 2012).

The aim of this systematic review and meta-analysis was to investigate the effectiveness of pharmacological and non-pharmacological treatments for the management of anxiety in community dwelling people living with dementia, including those living at home or in supported accommodation, attending outpatient clinics or in care homes. The review does not include inpatients in hospital or acute settings, as these were felt to be a population with different characteristics.

2. Methods

2.1. Study design

A systematic review and meta-analysis of randomised controlled trials was conducted following the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines (Page et al., 2021). The review protocol was registered on PROSPERO (PROSPERO 2022 CRD42022314119).

2.2. Data sources and searches

Search strategies were developed with an information scientist (Appendix A) without language or date restrictions and included a systematic literature search of EMBASE, MEDLINE, PsychINFO and EBSCO CINAHL from inception to January 26, 2023. The search strategy included terms to identify studies of dementia and subtypes of dementia (e.g., Alzheimer's disease), anxiety and subtypes (e.g., generalised anxiety disorder), and randomised controlled trials (RCTs). Reference lists of eligible reports were reviewed, and authors contacted to supplement incomplete reports of the original papers. An example search strategy can be found in Appendix A.

We included RCTs, and pilot or feasibility studies if randomisation of participants occurred, and appropriate findings provided. The intervention could be compared to a passive control (e.g, placebo or care as usual), an active control, or to more than one comparison group which could use active or passive control conditions. We excluded other quasi-experimental designs or if there were uncontrolled comparisons/ no comparator group.

2.3. Eligibility criteria

Included studies were RCTs of any pharmacological (e.g. antidepressants, antipsychotics, etc.) and non-pharmacological interventions (e.g. CBT, aromatherapy, etc.) directed at treating anxiety in people living with dementia. Searches were not restricted to the English language, but full texts were due to limitations of resources for translation, which meant we could report from the abstracts on potentially eligible papers that were excluded.

These studies have also to be conducted in the community or primary care, specifically with individuals living at home or in supported accommodation (sheltered or extra-care housing), attending outpatient clinics or in care homes (including nursing homes). RCTs not conducted in the community/primary care were excluded, specifically acute or in-patient settings.

The majority of study participants (above 60%) must have had anxiety at baseline or the mean score at baseline representing clinically significant anxiety. We used an inclusive approach and included studies that used validated and non-validated measures of anxiety in a dementia population. For scales with no validated/commonly used threshold for defining a 'case' of anxiety, the team discussed what cut off should be used, based on clinical expertise. For example, for the Neuropsychiatric Inventory Questionnaire (NPI) it was decided to include studies where the overall mean anxiety score for the groups were 3 or above and to conduct a sub-analysis for studies where the overall score was 6. We did not exclude people who also had other BPSD, e.g., depression, as BPSD symptoms can often co-exist and interventions usually focus on BPSD more generally than specific BPSD symptoms.

Patients must have been diagnosed with dementia, based on clinical records and diagnostic classification criteria, including Diagnostic and Statistical Manual of Mental Disorders (DSM), National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (NINCDS/ADRDA). Subtypes included: Alzheimer's type, vascular dementia, frontotemporal dementia, Parkinson's dementia and Lewy Body dementia. Those without a diagnosis of dementia were excluded, including those with mild cognitive impairment and those with rarer types of dementia, e.g., Pick's disease, Huntington's dementia and HIV-related dementia. Alcohol-related dementia was also excluded, as these are populations with different characteristics. People were of all ages and dementia severities were included, as measured by scales such as the Mini Mental State Examination (MMSE).

2.4. Study selection

DN screened all titles, abstracts, and full-text articles reporting potentially eligible studies. NA and AB independently screened 20% of titles and abstracts (40% in total) and 30% and 10% of all full-text articles (40% in total) respectively. We calculated the Cohen's κ statistic to assess interrater agreement regarding eligibility. An inclusive approach was taken, with disagreements arbitrated by KW when necessary. An online systematic review software (Rayyan, QCRI) facilitated literature screening (Ouzzani et al., 2016).

2.5. Data extraction

DN used a data extraction table for included studies and 20% were checked by NA and AB (40% in total). The table covered aims, research design, sample size, setting, participant demographics, type of dementia, severity of dementia, method for establishing dementia diagnosis, eg DSM, if and what criteria were used to diagnose anxiety/depression and risk of bias. Also, intervention characteristics (e.g., to whom the intervention was directed (e.g., patient, caregiver (carer), clinician, and surrounding environment), and details of the intervention (e.g., study

duration, who delivered the intervention and medication dosing schedule).

2.6. Risk of bias assessment

DN assessed all included articles using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (Sterne et al., 2019) and NA and AB independently assessed 10/31 and 6/31 of articles (16/31 in total). Domains cover bias arising from: the randomisation process (D1), deviations from the intended intervention (D2), missing outcome data (D3), measurement of the outcome (D4) and in the selection of the reported results (D5) (Sterne et al., 2019). Studies were assigned an overall score: "low", "some concerns" or "high". Disagreements were resolved through discussion with a third reviewer (KW) where necessary to achieve consensus. No article was excluded based on its quality assessment, but assessments were used to prioritise studies with lower risk of bias in our synthesis.

2.7. Data synthesis, analysis and quality of evidence

Meta-analysis was undertaken for studies using similar interventions. Results were pooled if two or more studies of a drug group were available. This included studies focused on groups of medication/supplements, non-pharmacological interventions aimed at individuals or groups. We grouped non-pharmacological interventions as follows:

Music therapy – the use of music and its elements as an intervention, for example, being played music or using instruments to create sounds/music.
Sensory stimulation – rousing one or more of the senses to evoke positive emotions, for example, by touching objects such as dolls.
Cognitive approaches – techniques used to encourage people to think or act differently, for example, cognitive behavioural therapy.
Muscular approach – techniques that involve touching, massaging or manipulating parts of the body.
Stimulating cognitive and physical activities – complex interventions using a combination of physical and cognitive activities, for example, tailored exercises.

Further sub-group analyses were performed according to setting (care home or if people lived in their own homes). For the remainder, a narrative synthesis approach was taken.

For meta-analysis, we estimated the standardised mean difference (Hedges g) from each study, then used random-effects meta-analysis to estimate the pooled estimate. Mean difference between intervention and control interventions at the primary end point was used in the meta-analysis, as this data was available for most studies. If multiple measures for anxiety were used in a study, the primary outcome was used regardless of validity. If more than one measure was used as a primary outcome, the most reliable and valid instrument used in a dementia population was chosen by consensus of the research team. If the standard deviation was not recorded, if possible it was estimated by using relevant information (including sample size and the standard error or confidence interval).

Heterogeneity was assessed using the I^2 statistic with an $I^2 > 50\%$ representing substantial heterogeneity. We used Review Manager software version 5.4 (Cochrane). The Grading of Recommendations Assessment, Development and Evaluation framework was used to summarize the quality of evidence (Guyatt et al., 2008). When studies compared multiple interventions to care as usual or placebo, a sensitivity analysis was performed where only one comparison was made at random to see if this affected results.

3. Results

Our search identified 7311 citations related to treatments in the management of anxiety in community dwelling people living with dementia. Out of this, 279 potentially eligible articles were retrieved for screening of full text and subsequently 31 studies were included in the review (Fig. 1), of which 22 were incorporated in a meta-analysis. One non-English full text paper was excluded due to language. There was substantial agreement between reviewers at the title and abstract stage ($k = 0.81$) and full-text review stage ($k = 0.87$).

3.1. Study characteristics

We included 31 studies (comprising 2747 participants) conducted between 1982 - 2023 (see Tables 1–3). They covered a wide range of interventions and are categorised as supplements and pharmacological interventions ($n = 9$), non-pharmacological group interventions ($n = 10$) and non-pharmacological interventions delivered to individuals ($n = 12$). Non-pharmacological interventions were also categorised according to intervention type: music therapy, cognitive approaches, muscular approaches, sensory stimulation and stimulating cognitive and physical activities. Names and details of each intervention are seen in Table 2&3. All but one paper, which was a PhD thesis (Andretta, 2008), were published in peer-reviewed journals. For most studies, the primary objective was to improve behavioural and psychological symptoms, with only three studies focused on reducing anxiety specifically (Moretti et al., 2004; Andretta, 2008; Spector et al., 2015). Tables 1–3 summarise the characteristics of the included studies.

People living with any type of dementia were eligible to participate in 18 studies, while nine studies included people living with Alzheimer's disease only (Andretta, 2008; Mintzer et al., 2001; Leonpacher et al., 2016; Akhgarjand et al., 2022; Giovagnoli et al., 2017; Lin et al., 2015; Suhr et al., 1999; Guetin et al., 2009; Menengic et al., 2022), one study people with vascular dementia only (Moretti et al., 2004) and four studies people with Alzheimer's disease and/or vascular dementia (Suh et al., 2006; Scripnikov et al., 2007; Nacu and Hoerr, 2016; Raglio et al., 2008). Most studies included participants with any severity of dementia, while four studies included only people with moderate to severe dementia. The Mini-Mental State Examination (MMSE) and Clinical Dementia Ratings (CDR) were mostly used to assess dementia severity but two studies used the TE4d-cog (Scripnikov et al., 2007; Nacu and Hoerr, 2016), one used the Functional Assessment Staging Tool (FAST) (Akhgarjand et al., 2022) and another also utilised the short cognitive performance test (SKT) and cognitive test battery clock-drawing test (CDT) (Nacu and Hoerr, 2016).

Studies took place in most continents (North America, South America, Europe, Oceania, and Asia) but not Africa. Four were conducted in low- and middle-income countries, including Brazil, Iran, Turkey and Ukraine. Fifteen studies were conducted in nursing homes or residential care facilities, 12 were in outpatient settings, two were conducted both in the participant's home and in outpatient settings, one was conducted in the participant's home and one online. Sixteen studies reported data on socioeconomic status, either the number of years in education, literacy rates, age participants left education or class related to occupation. Most of these studies reported on the average number of years in education, which ranged from 5.8 – 12 years (Raglio et al., 2008; Kolanowski et al., 2011). Only six studies reported ethnicity, which reported 66 - 96% of the sample population was White (Stanley et al., 2013; Andretta, 2008; Spector et al., 2015; Noone et al., 2022). Cost data was only reported in four studies, and only one of these covered cost in detail (Spector et al., 2015). In total, 20 different scales were used to measure anxiety and 17 studies used measures of anxiety that have been validated in a dementia population. Finally, primary endpoints ranged from four to 24 weeks. Table 4 summarises how each measure is used in practice, if they are validated in a dementia population and if they are designed for completion by patients, caregivers or professionals.

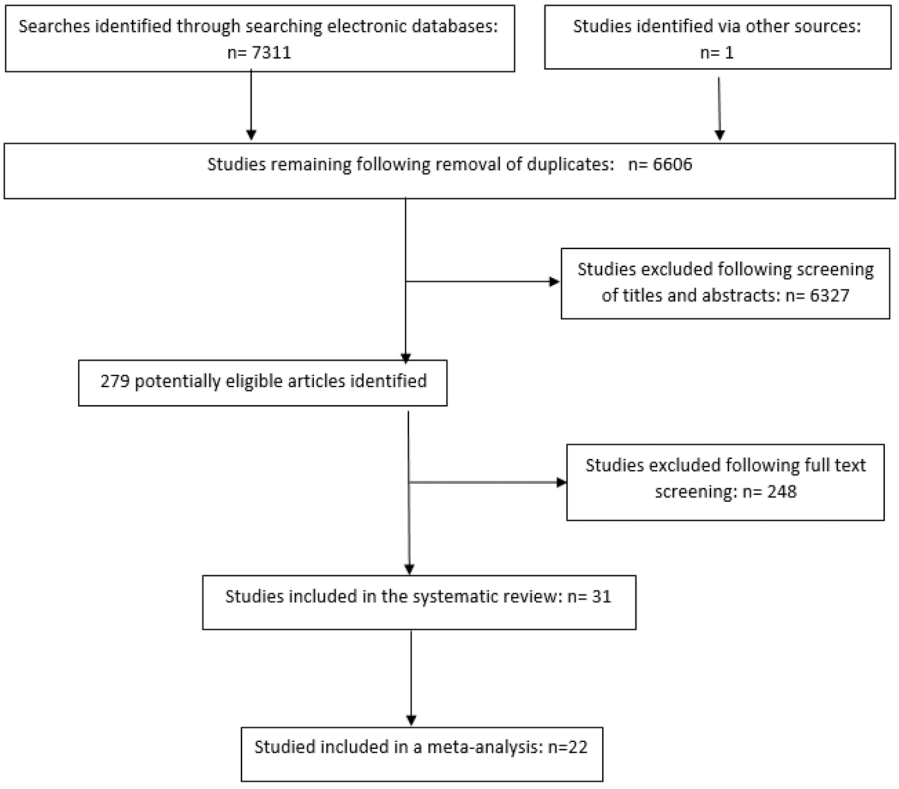

Fig. 1. Result of searches.

3.2. Quality assessment and quality of evidence

According to RoB 2, 9/31 studies had an overall 'low' risk of bias and 22/31 studies scored either 'some concern' or 'high' risk of bias (Appendix B). This was mostly due to the use of anxiety measures not validated in a dementia population, linked to the risk of bias in measurement of the outcome (D4) and not explicitly stating that the allocation sequence was concealed prior to group allocation, linked to risk of bias arising from the randomization process (D1). For some interventions that were 'psychosocial', it was not possible for participants to be blinded due to the nature of the intervention. However, many non-pharmacological studies did not specify if blinding had occurred or not. Few of the studies showed baseline differences between intervention groups. Risk of bias due to deviations from the intended interventions was deemed to be low for most studies (D2). Data for the outcome was available in most studies for most participants that had been randomised, the risk of bias due to missing outcome data was therefore low (D3). Related to risk of bias in selection of the reported result (D5), most of the studies analysed data in accordance with a pre-specified plan and usually only one measure was used for the outcome of interest.

3.3. GRADE assessment

The GRADE judgements are outlined in Appendix C. The certainty of evidence was low for all intervention categories. This was due to high risk of bias for many of the studies in all intervention types. Furthermore, many studies used measures not validated in a dementia population. In relation to consistency, for non-pharmacological interventions there was high heterogeneity (68%) and small sample sizes. When assessing indirectness for the non-pharmacological groups, the majority of confidence intervals overlapped and there was consistent direction of travel, in favour of the intervention groups. For precision, there were similar populations across most studies. Although most supplements/pharmacological interventions demonstrated the experimental group was effective compared to control groups, some studies did not provide any between group comparisons; and there were also significant differences between groups. Thus, a meta-analysis was not possible.

Intervention details and results are categorised below according to intervention category.

4. Supplements and pharmacological interventions

Nine studies investigated pharmacological/supplements with total participant numbers ranging from 28 - 404 and study duration (including follow up) ranging between six and 24 weeks. Mean age in the studies ranged from 64 to 83 years and four included participants living in a nursing home. The most often used measure of anxiety was the NPI, which was used in three studies. Meta-analyses could not be performed due to studies' heterogeneity. Further details can be seen in Table 1.

4.1. Gingko Biloba

Scripnikov et al. (n = 400) and Nacu et al. (n = 410) both compared 240 mg Ginkgo biloba extract (a supplement) with placebo over 22 and 24 weeks respectively in participants living with Alzheimer's or vascular dementia, using the NPI to measure anxiety (Scripnikov et al., 2007; Nacu and Hoerr, 2016). These were secondary analyses of drug-sponsored trials. Nacu et al. reported a reduction in mean anxiety score compared to baseline in both the intervention, − 1.1 (2.0) and control group, − 0.6 (1.9), and the difference between the groups was significant (p = 0.004). Scripnikov et al. also reported a mean reduction in anxiety score in the experimental group but no change in mean score for the control group. There was, however, no data on standard deviations or effect size. Standardised between group mean difference was not reported and could not be obtained by authors or calculated accurately as the data was only presented as a graph. There is therefore some evidence that Ginkgo biloba was effective in decreasing anxiety

Table 1
Study characteristics for supplements/pharmacological interventions.

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
(Moretti et al., 2004); Italy	People with mild to moderate vascular dementia; Outpatients	Mean age 75 yrs, female 52%, ethnicity NA, SES mean 8.7 yrs of education	N = 94; all completed the study	Olanzapine 2.5-5 mg/day Vs bromazepam 0.25%, 15 drops tds (control); study period 6 months; open study	BEHAVE-AD; at baseline and at **6 months**	Anxiety item in BEHAVE-AD olanzapine Mean score Pre 10.72 (1.54) control Mean score Pre 10.95 (1.45)	Anxiety item in BEHAVE-AD olanzapine Mean change score − 8.17 (1.12) control Mean change score − 0.04 (0.01) **p < 0.01** olanzapine versus the control group Overall BEHAVE-AD score olanzapine Mean change score − 16.95 (0.52) control Mean change score + 5.38 (0.01) **p < 0.01** olanzapine versus the bromazepam group Results unadjusted
(Mintzer et al., 2001); USA	People living with Alzheimer's (any severity); Nursing home	Mean age 82 yrs; 71% female; ethnicity: 95% white; SES NA	N = 206; a subset of the sample with anxiety was investigated separately (N = 120) and all were included in the analysis	Olanzapine 5 mg, 10 mg or 15 mg per day vs placebo; over 6 weeks; double blind RCT	NPI-NH; at baseline and weekly for 6 weeks, **last observation carried forward**	Anxiety subset olanzapine 5 mg N = 36 Mean score Pre 7.42 (3.13) olanzapine 10 mg N = 30 Mean score Pre 7.73 (3.06) olanzapine 15 mg N = 27 Mean score Pre 6.93 (3.28). control N = 27 Mean score Pre 6.74 (3.13)	Anxiety subset olanzapine 5 mg N = 36 Mean change in score − 3.72 olanzapine 10 mg N = 30 Mean change in score − 2.6 olanzapine 15 mg N = 27 Mean change in score − 2.1 control N = 27 Mean change in score − 1.67 Olanzapine 5 mg had significant improvements in anxiety compared to placebo: − 3.72 vs − 1.67, **p = 0.03** Results unadjusted
(Barnes et al., 1982); USA	People living with dementia (any severity); Nursing home	Mean age 83, age NA; sex NA; ethnicity NA; SES NA	N = 60; N = 53 included in final analysis	Loxapine vs thioridazine vs placebo; mean daily doses was 10.5 mg of loxapine, 62.5 mg of thioridazine, and 2.5 capsules of the placebo; study period 8 weeks; Double blind RCT	BPRS and SCAG; at weeks 1, 2, 4, 6, **8**	SCAG Mean score Pre for all groups 3.25 BPRS Mean score Pre for all groups 3.02 No standard deviations reported	SCAG Mean score Post control 3.04, loxapine 1.99, thioridazine 2.74. BPRS Mean score Post control 2.73, loxapine 1.98, thioridazine 2.59. Improvement in the loxapine group was significantly greater than in the placebo group for anxiety (p < .0.05) No standard deviations reported Results adjusted for differences among groups in baseline ratings
(Leonpacher et al., 2016); USA & Canada	People living Alzheimer's (any severity); Outpatient	Mean age NA; sex NA; ethnicity NA; SES NA	N = 186; N = 169 included in final analysis	Citalopram vs placebo; 30 mg/day citalopram; study period 9 weeks; Double blind RCT	NPI; at baseline, and weeks 3, 6 and **9**	citalopram Pre N = 61 (65%), median 4 (3,6) placebo Pre n 60 (65%), median 6 (3,8),	citalopram Post n = 36 (42%) placebo Pre Post n = 54 (65%) Those in the intervention group were less likely to have anxiety at week 9, compared to the control group: **OR 0.43, CI 0.22,**

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Table 1 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
							0.84, p = 0.01 Results adjusted for baseline symptoms and MMSE score
(Cantillon et al., 1996); USA	People living with mild dementia; Nursing home	Mean age 79 yrs, 68% female, ethnicity NA; SES NA	N = 28; N = 26 included in final analysis	5 mg Buspirone tds vs 0.5 mg haloperidol tds; Study period 10 weeks; Pilot double blind RCT	ASI; at baseline and **10 weeks**	haloperidol Mean score Pre 28.9 (2.51) buspirone Mean score Pre 29.46 (2.60)	haloperidol Mean score Post 28.42 (2.00) buspirone Mean score Post 26.22 (3.02) Greater deceases of anxiety levels in the buspirone group (11.1% mean reduction vs 2.1%, F= 7.43, p < 0.05) Results unadjusted
(Suh et al., 2006); South Korea	People living with Alzheimer's or vascular (any severity); Nursing home	Mean age 81 yrs; 72% females; ethnicity NA; SES NA	N = 120; N = 111 included in final analysis	Risperidone 0.5-1.5 mg/day vs haloperidol 0.5-1.5 mg/day; 18 weeks crossover RCT	BEHAVE-AD-K (specifically Godot syndrome and other anxieties); at baseline, week 2, 4, 6, **8**	Godot syndrome haloperidol Mean score Pre 1.26 (0.06), risperidone Mean score Pre 1.3 (0.06), Other anxiety haloperidol Mean score Pre 0.83 (0.06), risperidone Mean score Pre 0.91 (0.06),	Godot syndrome haloperidol Mean score Post 1.06 (0.06) risperidone Mean score Post 0.98 (0.05) Other anxiety haloperidol Mean score Post 0.69 (0.05) risperidone Mean score Post 0.61 (0.05) Risperidone was significantly more effective compared to haloperidol Godot syndrome (Z = −3.74, **p = 0.0002**), and other anxieties (Z = −2.62, **p = 0.0088**) Results adjusted for individual indicators
(Scripnikov et al., 2007); Ukraine	People living with Alzheimer's or vascular dementia (any severity); Outpatient	Mean age 64 yrs; 72% female; ethnicity NA; SES NA	N = 400; attrition information not presented	240 mg Ginkgo biloba extract vs placebo; study period 22 weeks; double blind RCT	NPI; at baseline, week 12 and **22**	Estimated mean score Pre ginkgo approx.3.2 vs placebo approx. 3.6	Estimated mean change from baseline ginkgo approx. − 1.2 vs control approx.0 Between group differences not reported Adjustment details not reported, assume results are unadjusted
(Nacu and Hoerr, 2016); Belarus	People living with Alzheimer's or vascular dementia (any severity); Outpatients	Mean age 65 yrs; 69% female; ethnicity NA; SES NA	N = 410; 402 included in the analysis	Ginkgo biloba extract vs placebo; 240 mg ginkgo for 24 weeks; study period 24 weeks; Double blind RCT	NPI; at baseline, 12 weeks and **24 weeks**	Mean score: Pre ginkgo 3.4 (2.3) Vs Pre placebo 3.2 (2.4)	Mean score: Post ginkgo 2.3 (2.1) vs placebo 2.7 (2.2) Ginkgo was significantly more effective compared to placebo (p = 0.004) Adjustment details not reported, assume results are unadjusted
(Akhgarjand et al., 2022); Iran	People living with mild to moderate Alzheimer's disease; Outpatients	Mean age 68 yrs; 47% female; ethnicity NA; SES 81% illiterate	N = 90; all included in the analysis	Supplements: lactobacillus rhamnosus HA-114, and bifidobacterium longum R0175 vs placebo, taken twice a day; study period 12 weeks; Double blind RCT	GAD-7; at baseline and at 12 weeks	Mean score: Pre L HA-11411.50 (2.20) vs B R0175 11.73 (2.47) vs placebo 10.00 (1.42)	Mean score: Post L HA-114 6.97 (1.15) vs B R0175 7.33 (1.18) vs placebo 12 (2.81) The GAD-7 scale significantly improved after supplementation with probiotics compared with the placebo (PTime x Group < 0.0001). lactobacillus rhamnosus: − 6.44, 95% CI: − 7.77 to − 5.12, bifidobacterium longum: − 6.26, 95% CI: − 7.59 to − 4.93.

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Table 1 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
							Results adjusted for education, type of Alzheimer's disease, BMI, and acetylcholinesterase inhibitors

[a] The primary end points are in bold.

symptoms in people living with dementia compared to placebo, although we were unable to calculate between group differences in one study (Scripnikov et al., 2007). Both studies were assessed as 'low' risk of bias.

4.2. Antidepressant drugs

Leonpacher et al. compared citalopram 30 mg/day (an antidepressant) with placebo over 9 weeks in 186 people living with Alzheimer's and the NPI was used to measure anxiety (Leonpacher et al., 2016). The proportion of participants with anxiety at baseline was 65% for both groups and at 9 weeks this was 42% (n = 36) for citalopram and 65% (n = 54) for placebo. Those in the citalopram group were less likely to have anxiety at week 9, compared to the control group: OR 0.43, CI 0.22, 0.84, p = 0.01. This study suggests citalopram was effective in decreasing anxiety symptoms in people living with dementia compared to placebo. This study was assessed as 'low' risk of bias.

4.3. Antipsychotic drugs

Five studies focused on antipsychotics, two of which had an overall 'low' risk of bias (Mintzer et al., 2001; Suh et al., 2006) and three a 'high' risk of bias (Moretti et al., 2004; Barnes et al., 1982; Cantillon et al., 1996). Moretti et al., 2004 (n = 94) and Mintzer et al., 2001 (n = 120) investigated olanzapine (an antipsychotic). Moretti et al. compared olanzapine 2.5–5 mg/day with bromazepam 0.25% 15 drops three times a day (a benzodiazepine used as a control) in an open study over 6 months in people living with vascular dementia. The Behavior Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) score was used, and anxiety was assessed as an individual item on the instrument. There was a greater reduction in mean score after 6 months in the olanzapine group (−8.17 (1.12)), compared to the control (bromazepam) group (−0.04 (0.01)) and the differences in mean change in score between the two groups was significant (p < 0.01). Mintzer et al. compared olanzapine 5 mg, 10 mg or 15 mg per day with placebo in a RCT over 6 weeks and the Neuropsychiatric Inventory- Nursing Home version (NPI-NH) was used to measure anxiety in people with Alzheimer's disease. It was a drug-sponsored post-hoc subgroup analysis, which found a reduction in mean score for all groups and the greatest mean change in score was seen in the olanzapine 5 mg group. The olanzapine 5 mg group had significant improvements in anxiety compared to placebo: − 3.72 vs − 1.67, p = 0.03. These studies suggest that, compared to bromazepam and placebo, olanzapine was effective in decreasing anxiety symptoms in people living with dementia.

Two studies investigated haloperidol with another medication (Cantillon et al., 1996; Suh et al., 2006). Cantillon et al. compared buspirone 15 mg/day (an anxiolytic) with haloperidol 1.5 mg/day (an antipsychotic) over 10 weeks, using the Anxiety State Inventory (ASI) to measure anxiety. This was a small study with 28 participants living with dementia and there were greater deceases of anxiety levels in the buspirone group (11.1% mean reduction vs 2.1%, F= 7.43, p < 0.05). Suh et al. investigated risperidone 0.5–1.5 mg/day vs haloperidol 0.5–1.5 mg/day (both anti-psychotics) in an 18-week crossover RCT with 120 participants living with Alzheimer's or vascular dementia, using the Behavior Pathology in Alzheimer's Disease Rating Scale, Korean version (BEHAVE-AD-K) to measure anxiety. Risperidone was significantly more effective compared to haloperidol in treating Godot syndrome (Z = −3.74, p = 0.0002), and other anxieties (Z = −2.62, p = 0.0088). Godot syndrome is anxiety related to upcoming events. These studies suggest haloperidol is not as effective as buspirone or risperidone in treating anxiety in people living with dementia.

One RCT compared a daily mean dose of the antipsychotic drug loxapine (10.5 mg) with thioridazine (62.5 mg, also an antipsychotic) and placebo; over a study period of 8 weeks in 60 participants living with dementia (Barnes et al., 1982). Barnes et al. used two instruments, the Brief Psychiatric Rating Scale (BPRS) and Sandoz clinical assessment geriatric scale (SCAG), to measure anxiety. Improvement in the loxapine group was significantly greater than in the placebo group for anxiety (p < 0.05). Using the SCAG, the mean score post intervention was 3.04 in the control group, 1.99 in the loxapine group and, 2.74 in the thioridazine group; standard deviations were not reported and could not be obtained from the authors. This study suggests compared to placebo, loxapine was effective in decreasing anxiety symptoms in people living with dementia.

4.4. Probiotics

Akhgarjand et al. compared two supplements (Lactobacillus rhamnosus HA-114, and Bifidobacterium longum R0175) with placebo over 12 weeks with 90 participants and Generalised Anxiety Disorder Assessment (GAD-7) was used to measure anxiety (Akhgarjand et al., 2022). Anxiety scores significantly improved after supplementation with probiotics compared with the placebo (PTime x Group < 0.0001); Lactobacillus rhamnosus: − 6.44, 95% CI: − 7.77 to − 5.12, Bifidobacterium longum: − 6.26, 95% CI: − 7.59 to − 4.93. This study was assessed as 'high' risk of bias.

5. Non-pharmacological interventions

Meta-analyses were conducted for non-pharmacological interventions according to intervention type combining interventions targeted at groups and individuals, if there were two or more studies:

1. Music therapy (n = 3)
2. Sensory stimulation (n = 4)
3. Cognitive approaches (n = 5)
4. Muscular approach (n = 4)
5. Stimulating cognitive and physical activities (n = 6)

Table 2
Study characteristics for non-pharmacological group interventions.

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
(Ikemata et al., 2017); Japan	People with mild to moderate dementia; living in group homes	Mean age 87 yrs; 81% female; ethnicity NA; SES NA	N = 37; all included in final analysis	**Muscular approach**: Muscle relaxation vs usual activities;15 mins for 90 consecutive days, delivered by staff/ researchers; study period 90 days; single blind RCT	NPI-NH; at baseline, at 30 days and **90 days**	Relaxation Mean score Pre 1.22 (1.70), Usual care Mean score Pre 1.32 (1.49), Adjustment details not reported, assume results are unadjusted	Relaxation Mean score Post 0.28 (0.67) Usual care Mean score Post 1.00 (1.45) Adjustment details not reported, assume results are unadjusted
(Eggermont et al., 2009); Netherlands	People with mild to severe dementia; Nursing home	Mean age 85 yrs; sex NA; ethnicity NA; SES na NA	N = 66; N = 61 included in final analysis	**Muscular approach:** Hand motor therapy vs group conversation and story reading (control group); 30 min, 5 days a week, during a period of 6 weeks; delivered by recreational therapists; study period 12 weeks; cluster trial	SCL-90; at baseline, **6 weeks** and 12 weeks	Hand motor therapy Mean score Pre 15.18 (4.87), Control Mean score Pre 15 (6.21), Mixed model *F* and *p* values not significant but depression was joined with anxiety Adjustment details not reported, assume results are unadjusted	Hand motor therapy Mean score **T1 (6 weeks) 13 (3.12)**, T2 (12 weeks) 12.57 (3.18) Control Mean score **T1 14.69 (6.25)**, T2 14.31 (7.17) Mixed model *F* and *p* values not significant but depression was joined with anxiety Adjustment details not reported, assume results are unadjusted
(Giovagnoli et al., 2017); Italy	People living with mild to moderate Alzheimer's dementia; Outpatient	Mean age 73 yrs; 62% female; ethnicity na; SES mean 8 yrs of education	N = 50; N = 39 included in final analysis	**Cognitive approach**: Cognitive training vs active music therapy vs neuroeducation; including two 45-min group sessions a week; over 3 months; coordinated by a neuropsychologist; single blinded RCT	STAI Y-1 & STAI Y-2; at baseline, **week 12** and week 24	STAI Y-1 Cognitive training Mean score Pre 43.58 (7.78), Active music therapy Mean score Pre 36.49 (10.66), Neuroeducation Mean score Pre 44.7 (10.52). STAI Y-2 Cognitive training Mean score Pre 43 (6.26), Active music therapy Mean score Pre 45.55 (17.37), Neuroeducation Mean score Pre 46 (9.23).	STAI Y-1 Cognitive training Post mean score 40.18 (8.58) Active music therapy Post mean score 40.73 (5.36) Neuroeducation Post mean score 35.85 (6.65) Time* group interaction [Pillai's trace = 0.30, F(4) = 3.22; **p = 0.017**] due to a decrease of state anxiety in the neuroeducation group at 12 weeks in comparison with baseline. STAI Y-2 Cognitive training Post mean score 39.2 (6.68) Active music therapy Post mean score 42 (4.3) Neuroeducation Post mean score 39.71 (4.35) Significant influence for time on the STAI Y-2 [Pillai's trace = 0.19, F(2) = 3.98**; p = 0.028**] due to a decrease of trait anxiety in all groups at 12 weeks. Adjustment details not reported, assume results are unadjusted
(Noone et al., 2023); UK	People living with mild dementia and carers; Outpatients	Mean age 77 yrs; sex 75% female; ethnicity: 17/20 white; SES on avg 12 yrs of education	N = 20; all included in final analysis	**Cognitive approach**: Psychoeducation and Mindfulness Based Interventions (MBI) vs treatment at usual; 90 min weekly sessions for 8 weeks; pilot single blinded RCT	RAID, GAD-7; at baseline and post treatment (2 weeks before and after the intervention)	RAID MBI Mean score Pre 12.1 (5.2), Vs TAU Pre 14.3 (9.26) GAD-7 MBI Mean score Pre 8.70	RAID MBI Mean score Post 12.67 (7.2) Vs Post 13.0 (7.32) GAD-7 MBI Mean score Post 8.60 (6.53) Vs Post 7.11 (6.49)

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Table 2 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
						(8.23) Vs TAU Pre 9.22 (6.28)	Mixed Between-Within Subjects ANOVAs, there were no significant interactions between time and group, no significant main effect of group, no significant main effect of time Adjustment details not reported, assume results are unadjusted
(Raglio et al., 2008); Italy	People living with moderate to severe Alzheimer's or vascular dementia; Nursing homes	Mean age 85 yrs; 84.5% female, ethnicity NA; SES mean 5.8 yrs education	N = 59; all included in final analysis	**Music therapy**: Music therapy vs education & entertainment (control); A non-verbal approach was taken, using rhythmical and melodic instruments to promote communication; over three cycles of 10 sessions (over 16 weeks); delivered by a music therapist; RCT	NPI; at baseline, week 8, 16, 20	Music therapy Mean score Pre 3, Control Mean score Pre 3.34,	Music therapy Mean score Post 1.5 Control Mean score Pre 3.34, Post 3.1 Adjustment details not reported, assume results are unadjusted
(Liu et al., 2021); Taiwan	Veterans living with mild to moderate dementia; Veterans home	Mean age 77 yrs; 67% female; ethnicity NA; SES mean 7 yrs of education	N = 50; all included in final analysis	**Music therapy**: Music therapy with percussion vs rest and reading (control) delivered by music facilitator; one hour a week for 12 weeks; double bind RCT	HAMA; at baseline, week 6 and 12	Music therapy Mean score Pre 13.36 (0.95), Control Mean score Pre 13.24 (0.97),	Music therapy Mean score T1 11.6 (1.23), Post 10.2 (1.94) Control Mean score T1 13.08 (1.22), Post 12.96 (1.21) Mean difference between the groups at week 6 (t = 4.277, **P < 0.001**) and week 12 (t = 6.048, **P < 0.001**) Adjustment details not reported, assume results are unadjusted
(Lin et al., 2015); China	People living with Alzheimer's (any severity); Outpatients	Mean age 42 yrs; 79% female; ethnicity: 100% Han Chinese; SES: 12% 9 years or more of education	N = 147; all included in final analysis	**Stimulating cognitive and physical activities:** GO game short time (SGGI) for 1 h a day vs GO game long time (LGGI) for 2 h a day vs Without GO game (control); GO game is similar to chess; delivered by GO- game staff; RCT	HADS; at baseline and **6 months**	SGGI Pre N = 44 (89.7%) had anxiety LGGI Pre N = 43 (87.8%) had anxiety Control Pre N = 42 (85.7%) had anxiety	SGGI Mean score Post mean 6.59 (4.11), change from baseline − 3.95 LGGI Mean score Post mean 5.89 (3.34), change from baseline − 4.12 Control Mean score Post mean 8.07 (4.26), change from baseline − 2.08 Post Mean difference between groups 1.75 (0.17 to 3.68), T test 2.22, **p = 0.034** Adjustment details not reported, assume results are unadjusted
(Cheung et al., 2022); ; Honk Kong	People living with mild to moderate dementia and carers; Outpatients and in their own home	Mean age 79.5 yrs; sex 52% female; ethnicity: na; SES 24% had no formal schooling	N = 100; all included in final analysis	**Stimulating cognitive and physical activities:** Music-with-movement (MM) intervention vs treatment as usual; 30-45 min sessions over 12 weeks; delivered by trained centre staff at the centre on weeks 1, 3, 7, and 12 and home visits by trained volunteers weeks 2, 5, and 9; cluster RCT	RAID; at baseline and post treatment at 12 weeks	MM Mean score Pre 11.53 (8.35) Vs Pre 12.47 (9.31)	MM Mean score Post 8.90 (7.12) Vs Post 11.92 (7.20) No difference in RAID scores between groups: (β = −3.08 SE= (1.72), p = 0.072 Adjusted for baseline arm differences
(Moyle et al., 2013); Australia	People living with mid to late dementia; residential aged care facility	Mean age 85 yrs; sex NA; ethnicity NA; SES NA	N = 18; all included in final analysis	**Sensory stimulation:** Sensory stimulation Robotic seal (PARO) vs reading control group; 45-minute sessions three afternoons a week for 5 weeks; there was a facilitator delivering the sessions; Sessions encouraged participants to	RAID; proxy RAID; OERS; at baseline, week 5 and 10	No data available before the intervention	Proxy RAID Mean score Post 12.8 (11.2) vs Post 17.1 (15.1). Cohen's d − 0.3, − 0.4 RAID Mean score Post 9.8 (6.5) vs Post 7

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Table 2 (*continued*)

Study details (Author; year; country)	Population details (Type and severity of dementia; setting)	Sample characteristics (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	Sample size and attrition details	Intervention & Comparator (Intervention details; study period)	Anxiety scale (Scale; and frequency used; **primary end point**)[a]	Results (mean baseline scores and standard deviations or median and interquartile range)	Results (**primary end point**, between group comparisons; adjustments)
				examine PARO while being passed around the group; pilot crossover trial			(6.9), Cohen's d + 0.4 Adjustment details not reported, assume results are unadjusted
(Andretta et al., 2008); USA	People living with Alzheimer's (any severity); Nursing home	Mean age 88 yrs; ethnicity: 96% white; SES na	N = 84; all included in final analysis	**Sensory stimulation:** Snoezelen treatment (auditory, visual, tactile and olfactory stimulation) vs no treatment; one 20 min session; facilitated by treatment facilitator; RCT	BAI; at baseline, post treatment, week 1 and **4**	Mean score Snoezelen Pre 17.07 (1.24), Vs Pre 18 (1.58),	Mean score Snoezelen Post 13.46 (3.82) Vs Post 16.21 (3.19) 4-week follow up difference between groups: t(78) = 3.47, **p < .001.** The main effect for the difference between the two groups was statistically significant, F(1, 76) = 128.20, **p < .001**. The main effect for time was also statistically significant, F(3, 228) = 79.32, **p < .001.** The interaction between group and time was statistically significant, F(3, 228) = 58.42, **p < .001** Adjustment details not reported, assume results are unadjusted

[a] The primary end points are in bold.

5.1. Music therapy

Three studies investigated music therapy (Raglio et al., 2008; Liu et al., 2021; Guetin et al., 2009). However, a meta-analysis could only be conducted with two studies, as Raglio et al. did not present standard deviations. In this study, music therapy was compared to an active control of 'education & entertainment' over 16 weeks in 59 participants with Alzheimer's or vascular dementia and NPI was used to measure anxiety (Raglio et al., 2008). Participants were in groups and there was a significant reduction in anxiety in the music therapy group (Pre 3, Post 1.5, F: 20.69, $P < 0.001$). There was a slight reduction in the control group but this was not significant (mean score Pre 3.34, Post 3.1, change in score F: 0.86, p value not stated). This study suggests music therapy is effective in reducing anxiety symptoms.

In the other two studies, participant numbers were 30 to 50 people, study duration ranged between 12 and 24 weeks and Hamilton Anxiety Rating Scale (HAMA) was used to measure anxiety. Liu et al., used music percussion in groups, facilitated by a music facilitator for one hour a week for 12 weeks and compared this to a rest and reading group. Guetin et al., also compared a rest and reading group to participants listening to a style of music of their choice that was streamed through headphones, once a week for 20 min over 16 weeks. Although the sample sizes are small, music therapy was effective in reducing anxiety in people living with dementia, compared to reading groups (Fig. 2). In the meta-analysis, the standardised mean difference was – 1.92 (CI: −2.58, −1.25). I^2 statistic was 24% representing substantial homogeneity.

5.2. Sensory stimulation

Four studies investigated sensory stimulation (Andretta, 2008; Moyle et al., 2013; Moyle et al., 2019; Pu et al., 2020), participant numbers ranged from 18 to 84 people and study duration ranged between three and 10 weeks. Two studies were group interventions (Andretta, 2008; Moyle et al., 2013) and two were delivered to individuals (Moyle et al., 2019; Pu et al., 2020). Andretta compared Snoezelen treatment (auditory, visual, tactile and olfactory stimulation) to no treatment, during a one 20-minute session that was facilitated by a treatment facilitator. Moyle et al., 2019., compared doll therapy to treatment as usual, where participants in a long-term facility were given a doll for 30 min three times a week for three weeks. Both Pu et al., and Moyle et al., used stimulation Robotic seals (PARO) as an intervention, but one was in a group setting and in the other study participants were given PARO in their room. PARO was given for 30–45 min three to five times a week for 5 and 6 weeks respectively.

In the meta-analysis, the standardised mean difference was – 0.21 (CI: −0.74, 0.33), thus sensory stimulation was not demonstrated to be effective in reducing anxiety in people living with dementia, compared to care as usual and a reading group (Fig. 3). I^2 statistic was 64% representing substantial heterogeneity.

5.3. Cognitive approaches

Five studies investigated cognitive approaches (Giovagnoli et al., 2017; Jenewein et al., 2021; Spector et al., 2015; Noone et al., 2022; Stanley et al., 2013). Participant numbers ranged from 20 to 54 people and the total study duration ranged between 10 and 24 weeks. Two studies were group interventions (Giovagnoli et al., 2017; Noone et al., 2022) and three were delivered to individuals (Jenewein et al., 2021; Spector et al., 2015; Stanley et al., 2013). Interventions included cognitive behavioural therapy (CBT), cognitive training, a mindfulness-based intervention and dignity therapy- this involved two interviews delivered by trained healthcare professionals to improve coping and emotional distress in people with early dementia. In these studies, sessions were usually weekly (except for dignity therapy) and delivered by a trained professional over 8- 24 weeks.

In the meta-analysis, the standardised mean difference was – 0.19

Table 3
Study characteristics for non-pharmacological interventions delivered to individuals.

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
(Jenewein et al., 2021); Switzerland	People with early dementia; Outpatients	Mean age 79 yrs; 57% female; ethnicity NA; SES mean 37% university educated	N = 54; N = 48 included in final analysis	**Cognitive approach**: Dignity therapy vs usual care; two interviews; delivered by trained healthcare professionals; study period 3 months; pilot RCT. Dignity therapy: this involved two interviews delivered by trained healthcare professionals to improve coping and emotional distress in people with early dementia.	HADS; at baseline, at 4 weeks **and 3 months**	Dignity therapy Mean score Pre 8.39 (5.976) Usual care Mean score Pre 8.69 (5.453)	Dignity therapy Mean score T1 (4 weeks) 8.19, **T2 (3 mo) 5.7 (4.780)** Usual care Mean score T1 10.08, **T2 6.72 (4.399).** No statistically significant group by time interaction effect: F = 0.71; df = 2, 70.3; P = 0.50 Adjustment details not reported, assume results are unadjusted
(Spector et al., 2015); UK	People living with mild to moderate dementia; Outpatient	Mean age 78.5 yrs; 60% female; mean 9.5 yrs of education; 96% white	N = 50; N = 39 included in primary end point analysis (21;18)	**Cognitive approach**: CBT vs usual care; One hour CBT over 10 sessions in 10 weeks intervention aimed at dyads (person with dementia and carer); delivered by clinical psychologists; pilot single blind RCT	RAID & HADS; At baseline, **week 15** and 6 months	Pre 100% of participants had anxiety **RAID** Mean score CBT Pre 18 (6), usual care Pre 21 (6) HADS Mean score CBT Pre 8 (4), usual care Pre 9 (5)	**RAID** Mean score CBT Post 13.57 (8.51), usual care Pre 17.89 (8.41) Results reported unadjusted and adjusted for baseline anxiety and cognition
(Stanley et al., 2013); USA	People living with mild to moderate dementia; at home	Mean age 79 yrs; 59% female; ethnicity 66% white; SES 53% college educated	N = 32, N = 26 included in final analysis (11 vs15)	**Cognitive approach**: Peaceful Mind (CBT) vs Usual care; weekly in home sessions and phone calls over 6 months; delivered by graduate-student clinicians and a predoctoral; pilot RCT	NPI; RAID; PSWQ-A; GAI; at baseline, 3 and **6 months**	**NPI** Mean score CBT Pre 4.8 (4.16), Vs Pre 4.6 (3.11) **RAID** Mean score CBT Pre 13.9 (6.9), Vs Pre 16.2 (8.24), PSWQ-A Mean score CBT Pre 16 (7.14), Vs Pre 18.8 (7.59), GAI Mean score CBT Pre 5 (5.58), Vs Pre 6.7 (6.10),	**NPI** Mean score CBT Post 1.5 (2.84) Vs Post 3.9 (3.83) **RAID** Mean score, CBT Post 11.9 (6.92) Vs Post 17.2 (9.89) PSWQ-A Mean score CBT Post 15.3 7.65) Vs Post 16.2 (7.87) GAI Mean score CBT Post 3.9 (3.57) Vs Post 4.2 (5.2) Treatment effects not significant at 6 months. Results adjusted for baseline scores
(Pu et al., 2020); Australia	People with any severity of dementia; Long term care facilities	Mean age 86 yrs; 70% female; ethnicity NA; SES NA	N = 43; all included in the final analysis	**Sensory stimulation:** Sensory stimulation Robotic seal (PARO) vs usual care; 30 mins with PARO Mon- Fri for 6 weeks in their rooms; non-facilitated; study period 6 weeks; pilot RCT	RAID; at baseline and after every session; **week 6**	PARO Mean score Pre 17.24 (11.95), Control Mean score Pre 20.18 (10.33),	PARO Post 14.76 (12.93), Control Post 19.18 (13.75). Adjusted mean difference between groups − 1.294 (−6.234, 3.645) was not significant (**P 0.608)** Results adjusted for baseline age, sex, cognitive status, and medications
(Moyle et al., 2019); Australia	People living with dementia (any severity); Long term facility	Mean age 88 yrs; 100% female; ethnicity NA; SES NA	N = 35; N = 33 included in final analysis (18,15)	**Sensory stimulation:** Doll therapy (a form of sensory stimulation) vs care as usual; They were given a doll for 30 mins x3 a week for 3 weeks; administered by	OERS; at baseline, week 1 and **week 3**	Doll therapy Mean score Pre 1.72 (1.45), Control Mean score Pre 1.53 (1.41),	Doll therapy Mean score Post 1.5 (1.2) Control Mean score Post 1.27 (1.03) Doll therapy not

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Table 3 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
				research assistant; study period 3 weeks; pilot RCT			effective. Mean change in score between groups not significant **p = 0.929** Adjustment details not reported, assume results are unadjusted
(Rodriguez-Mansilla et al., 2014); Spain	People with moderate to severe dementia; Residential homes	Mean age NA; sex NA; ethnicity NA; SES NA	N = 120; N = 111 included in final analysis (35, 40, 36)	**Muscular approach:** Ear acupressure vs relaxing massage vs usual care; study period 5 months; 3 months of active treatment, 2 months follow up; Double blind RCT. For ear acupressure different parts of the ear were stimulated, and adhesive herbal seeds used on the ears, which were replaced every 15 days, this was delivered by an acupuncturist and daily checks were made. This was compared to relaxing massage on the lower limbs and back for 20 min Monday to Friday delivered by a physiotherapist; and also to care as usual.	Campbell score; at baseline and every month during study; **5 months**	Massage therapy Mean score Pre 7.3 (2.6), Ear acupressure Mean score Pre 7.1 (2.2), Control Mean score Pre 6.6 (1.3),	Massage therapy Mean score Post 6.8 (2.3) Ear acupressure Mean score Post 7.2 (2.2) Control Mean score Post 8.8 (1.0) The mean score increased for the control group compared with other groups ($P < 0.001$) Adjustment details not reported, assume results are unadjusted
(Suhr et al., 1999); USA	People with Alzheimer's dementia (any severity); Outpatient	Mean age 74.5 yrs; sex NA; ethnicity NA; education to mean 15 yrs	N = 34; N = 29 included in final analysis (17, 12)	**Muscular approach:** Progressive muscle relaxation (PMR) vs taped imagery technique (control); aimed at people with dementia and carers; once weekly sessions designed to teach PMR; PMR is sequential tension and relaxation of various muscle groups throughout the body; delivered by a therapist; study period 2 months; RCT. The control group experienced taped multisensory imagery technique imaginal relaxation technique. This is an individualised multisensory imagery, which has been shown to be effective in older people with anxiety	BAI & BPRS; at baseline and **2 months**	BAI Mean score PMR Pre 8.2 (7.6), Vs Pre 9 (7.4) BPRS Mean score PMR Pre 34.8 (20.5), Vs Pre 38.3 (23.8),	BAI Mean score PMR Post 6.5 (7.1) Vs Post 6.8 (3.5) When comparing treatment groups there was no effect of treatment ($F< 1$), no effect of time ($F < 1$), and no interaction effect ($F < 1$) for self-report of anxiety symptoms BPRS Mean score PMR Post 26.8 (19.6) Vs Post 26.2 (11.7) When comparing groups there was a significant effect of time ($F = 12.68$, $P < .005$), with no treatment effect ($F < 1$) and no interaction effect ($F < 1$) Adjustment details not reported, assume results are unadjusted
(Guetin et al., 2009); France	People living with mild to moderate Alzheimer's; Nursing homes	Mean age 86 yrs; 73% female; ethnicity NA; SES: mean 43% labourers	N = 30; N = 26 included in final analysis (14, 12)	**Music therapy**: Music therapy vs rest and reading (control); In the group of patients undergoing music therapy, the sessions took place once a week for 20 mins over 16 weeks, participants listened to a style of music of their	HAMA; at baseline, week 4, 8, **16,** 24	Music therapy Mean score pre 22 (5.3), Control Mean score Pre 21.1 (5.6)	Music therapy Mean score post 8.4 (3.7) Variation –13.2 (5.2) Control Mean score Post 20.8 (6.2) Variation –0.9 (7.4) Mean change from baseline to 16 weeks

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Table 3 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
				choice that was streamed through headphones; follow up period of 6 months; RCT			between the groups **p < 0.001** Persistence of the effect of music therapy at 24 weeks 10.6 (6.3) vs 20.5 (5.4), **p < 0.001** Results unadjusted
(Oliveira et al., 2017); Brazil	People living with dementia (any severity); Outpatient	Mean age 78.7 yrs; 71% female, ethnicity NA; SES: avg 38% 8 yrs or more of education	N = 21, all included in final analysis	**Stimulating cognitive and physical activities:** Tailored activity program (TAP) vs psychoeducation (control group); eight sessions over 3 months; Activities were tailored to the individual and included activities of daily living, activities include washing dishes and playing with a ball; delivered by occupational therapists; pilot double blind RCT	NPI-C; at baseline and **3 months**	TAP Mean score Pre 11.55 (5.6) Control Mean score Pre 6.7 (7.1) Adjustment details not reported, assume results are unadjusted	TAP Mean score Post 7.36 (6.08), mean Control Mean score Post 8.1 (7.92), mean Statistically significant differences between the two groups in the presence of anxiety (**p = 0.02**) Adjustment details not reported, assume results are unadjusted
(Oliveira et al., 2017); Brazil	People living with moderate to severe dementia; Outpatient and at home	Mean age 77 yrs; 67% female; ethnicity NA; 30% 8 yrs or more of education	N = 54; N = 48 included in final analysis (25;23)	**Stimulating cognitive and physical activities:** Tailored activity program (TAP) vs psychoeducation (control group); eight sessions over 3 months; Activities were tailored to the individual and included activities of daily living, activities include washing dishes and playing with a ball; delivered by occupational therapists; double bind RCT	NPI-C; at baseline and **3 months**	TAP Mean score Pre 11.6 (8.0) Control Mean score Pre 10.3 (8.8)	TAP Mean score Post 6.8 (7.0), mean change − 4.4 (6.2), Control Mean score Post 10.2 (8.5), mean change - 0.1 (4.8) Group differences in changes between Pre and Post: effect size 0.4, **p = 0.007** Adjustment details not reported, assume results are unadjusted
(Kolanowski et al., 2011); USA	People living with dementia (any severity); Nursing home	Mean age 86 yrs; 76% female; ethnicity: 88% white; SES: mean 12 yrs of education	N = 128; N = 122 included in final analysis (28,33,30,31)	**Stimulating cognitive and physical activities:** Need-Driven Dementia-Compromised Behavior model (NDB) comprising 3 groups: activities tailored and adjusted to individuals according to either functional level (FL), personality style of interest (PSI) or both (FL&PSI). vs prescribed activities (control); Activities included arts and crafts, painting, and sorting beads. The active control group were prescribed activities that were opposite to their personality style and functional level; for 20 min twice per day (morning and afternoon) 5 days each week for 3 consecutive weeks; study period of 5 weeks (3 weeks of intervention and 1 week pre and post intervention); double blind RCT	ARS; at baseline, **during the 4 weeks of intervention** and week 5 (1 week after the intervention)	FL Least mean square Pre 1.79 (1.9-2.5), PSI Least mean square Pre 2.21 (1.9-2.6), FL&PSI Least mean square Pre 2.02 (1.7-2.4), Control Least mean square Pre 1.99 (1.7-2.3),	FL Least mean square During 1.6 (1.3-1.9) SD= 0.810 PSI Least mean square During 1.7 (1.4-2.0), SD= 0.878 FL&PSI Least mean square During 1.5 (1.2 – 1.8), SD= 0.838 Control Least mean square During 1.6 (1.3-1.9), SD= 0.852 Anxiety did not differ according to group during the intervention-Interest adjustment p = 0.9, function adjustment p = 0.27, interaction p = 0.45 Results adjusted for MMSE, Psychogeriatric Dependency Rating Scale (PGDRS), and years of education

(*continued on next page*)

Table 3 (*continued*)

Study details (Author; year; country)	**Population details** (Type and severity of dementia; setting)	**Sample characteristics** (Sample size; mean age; % female; ethnicity data; socioeconomic data (SES))	**Sample size and attrition details**	**Intervention & Comparator** (Intervention details; study period)	**Anxiety scale** (Scale; and frequency used; **primary end point**)[a]	**Results** (mean baseline scores and standard deviations or median and interquartile range)	**Results** (**primary end point,** between group comparisons; adjustments)
(Menengic et al., 2022); Turkey	People living with mild to moderate Alzheimer's; online	Mean age 79 yrs; 70% female; ethnicity: NA; SES: all could read	N = 20, all included in final analysis	**Stimulating cognitive and physical activities:** Motor-cognitive dual-task exercise treatment consisted of simple chair-based exercises; started with 15-minute sessions 5 days per week, and gradually progressed to 40-minute sessions, 4 days per week; attended 25 exercise sessions over 6 weeks supervised by a physical therapist; double blind RCT	BAI; at baseline and at week 6	Mean score Pre 12.1 (8.72), Vs Pre 8.4 (5.33)	Mean score Post 3.1 (5.02) Vs Post 14.9 (9.04) Mean difference and SE TG:− 9 ± 2.14 (- 23 to 1) CG 6.5 ± 2.32 (- 3 to 19) P = 0.001 Adjustment details not reported, assume results are unadjusted

[a] The primary end points are in bold.

(CI: −0.56, 0.18), thus cognitive approaches were not demonstrated to be effective in reducing anxiety in people living with dementia, compared to the control groups that were care as usual, neuro-education and music therapy (Fig. 4). I^2 statistic was 25% representing substantial homogeneity.

5.4. Muscular approaches

Four studies investigated a muscular approach (Eggermont et al., 2009; Ikemata and Momose, 2017; Rodriguez-Mansilla et al., 2015; Suhr et al., 1999), which included hand motor therapy, ear acupressure and relaxing massage. Participant numbers ranged from 34 to 120 people and study duration ranged between two and five months. Muscular approaches included relaxation, hand motor therapy and ear acupressure, where different parts of the ear were stimulated, and adhesive herbal seeds used on the ears. Two of the studies were group interventions (Eggermont et al., 2009, Ikemata and Momose, 207) and two were delivered to individuals (Rodriguez-Mansilla et al., 2015; Suhr et al., 1999). Interventions were delivered by therapists or trained staff/researchers.

In the meta-analysis, the standardised mean difference was − 0.65 (CI: −1.02, −0.28), showing muscular approaches were effective in reducing anxiety in people living with dementia, compared to the control groups that were care as usual, taped imagery technique, and a conversation and story group (Fig. 5). I^2 statistic was 53% representing substantial heterogeneity.

5.5. Stimulating cognitive and physical activities

Six studies investigated stimulating cognitive and physical activities (Kolanowski et al., 2011; Lin et al., 2015; Oliveira et al., 2021; De Oliveira et al., 2019; Cheung et al., 2022; Menengic et al., 2022), which included the GO game (similar to chess), music with movement, exercise treatment via home-based tele-rehabilitation, tailored activity programmes (focused around activities of daily living), Motor-cognitive dual-task exercise treatment (consisting of simple chair-based exercises); and a Need-Driven Dementia-Compromised Behavior model (NDB). NDB comprised of three groups: activities tailored and adjusted to individuals according to either functional level (FL), personality style of interest (PSI) or both (FL&PSI). Activities included arts and crafts, painting, and sorting beads. Participant numbers ranged from 20 to 147 people and study duration ranged between 5 and 24 weeks. The interventions were delivered by therapists. Two studies were group interventions (Lin et al., 2015; Cheung et al., 2022) and four were interventions delivered to individuals (Oliveira et al., 2021; De Oliveira et al., 2019; Kolanowski et al., 2011; Menengic et al., 2022).

In the meta-analysis, the standardised mean difference was – 0.31 (CI: −0.53, −0.09), showing stimulating cognitive and physical activities were effective in reducing anxiety in people living with dementia, compared to the control groups that were care as usual, prescribed activities and psychoeducation (Fig. 6). It is important to note that multiple comparisons were made for three studies, giving them excess weight in the meta-analysis. However, a sensitivity analysis was performed randomly excluding excess comparisons for these studies and the result did not alter. I^2 statistic was 37% representing substantial homogeneity.

Non-pharmacological interventions were also analysed according to whether they were group interventions or if they were delivered to individuals.

6. Non-pharmacological group interventions

Ten studies investigated non-pharmacological group interventions (see Table 2 for details).

All studies were parallel RCTs, except for one which was a pilot crossover trial (Moyle et al., 2013). They included between 18 and 147 participants and study durations ranged between 4 and 24 weeks. Three studies focused on people living with Alzheimer's and one with people with Alzheimer's or vascular dementia. A range of instruments was used to measure anxiety as shown in Table 2.

In a meta-analysis including non-pharmacological group interventions the standardised mean difference was – 0.44 (CI: −0.75, −0.14). I^2 statistic was 66% representing substantial heterogeneity. The results suggested that overall, non-pharmacological group interventions were effective in treating anxiety in people living with dementia compared to the control groups (Fig. 7). Although the samples were small, music therapy appeared to be effective and stimulating cognitive and physical approaches appeared to have a weak effect, while cognitive approaches appeared not to be effective. For Giovagnoli et al. only the results for the cognitive and neuroeducation were included in the meta-analysis, as our research team considered music therapy was not an active control (Giovagnoli, . et al., 2017). A sensitivity analysis was performed as more than one comparison was made for Lin et al. giving this study more weighting in the meta-analysis, the results did not differ

Table 4
Different measures used for anxiety.

Observed emotion rating scale (OERS)- Rates the extent or duration of five dimensions of affect (Pleasure, Anger, Anxiety/Fear, Sadness and General Alertness), observed over a ten-minute period, it has not been validated in dementia (Lawton Mp and Klapper, 1999).	**Symptom checklist 90 (SCL-90)-** Participants self- report on 90 items, including 10 items specifically on anxiety, each item is rated from 0 to 4, it has not been validated in dementia (L.R, 1994).	**Behavioural pathology in Alzheimer's disease (BEHAVE- AD)-** Caregivers are queried about BPSD. It consists of 25 symptoms grouped into seven categories. It has been validated in dementia (Reisberg et al., 1987).	**Penn State Worry Questionnaire for Adults (PSWQ-A)-** A 16-item self-reported scale designed to measure the trait of worry in adults. It has not been validated in dementia (Meyer et al., 1990).
Neuropsychiatry Inventory (NPI)- The questionnaire is administrated to the caregiver. It evaluates the frequency and severity of the symptom and the impact that each behaviour has on the caregiver. There are specific questions for anxiety. It has been validated in dementia (Cummings, 1997).	**Hamilton Anxiety Rating Scale (HAMA)-** The scale consists of 14 items, rated by the professional. It has not been validated in dementia (Maier et al., 1988).	**Geriatric Anxiety Inventory (GAI)-** Self-administered questions consisting of 20 "Agree/Disagree" items designed to assess typical common anxiety symptoms. It has been validated in dementia (Pachana et al., 2007).	**Generalised Anxiety Disorder Assessment (GAD-7)-** Self-reported seven item scale that has not been validated in dementia (Spitzer et al., 2006).
Neuropsychiatry Inventory for nursing homes (NPI- NH)- Adapted from the original NPI for residents in extended care facilities or other care settings, where information is gathered from professionals (Cummings, 2020).	**Brief Psychiatric Rating Scale (BPRS)-** Assesses the level of 18 symptom constructs, including anxiety, based on the professional's view of the patient. It has not been validated in dementia (Hunter and Murphy, 2011).	**The Sandoz clinical assessment-geriatric scale (SCAG)-** A seven-point scale, assessed by an interview/observation conducted by a professional. It has been validated in dementia (Venn, 1983).	**Hospital Anxiety and Depression Scale (HADS)-** A 14- item questionnaire that self-reports individuals' self-perceived levels of depression and anxiety, it has not been validated in dementia (Stern, 2014).
Neuropsychiatry Inventory- Clinician rating scale (NPI-C)- Adapted from NPI and allows the clinicians to participate in the rating (Cummings, 2020).	**State- Trait anxiety inventory (STAI)-** Form Y, its most popular version, has 20 items for assessing trait anxiety and 20 for state anxiety, it is self-reported and not been validated in dementia (Sydeman, 2018).	**Becks Anxiety Inventory (BAI)-** Self-report of symptoms using a scale of 21 items. It has not been validated in dementia (Beck et al., 1988).	**Behavioural pathology in Alzheimer's disease, Korean version (BEHAVE- AD-K)-** Adapted from BEHAVE-AD (Suh Gh et al., 2001).
Philadelphia Geriatric Centre Affect Rating Scale (ARS)- Direct observation of facial expression, body movement, and other cues. It has not been validated in dementia (Lawton et al., 1996).	**Rating Anxiety in Dementia (RAID)-** A professional interviews the carer and the person living with dementia. It includes 20 items on the scale and has been validated in dementia (Shankar et al., 1999).	**Anxiety state Inventory (ASI)-** A 16 item self-report questionnaire that has not been validated in dementia (Mcnally, 2002).	**Campbell Anxiety scale-** It assess the presence of anxiety and/or chronic pain in people who cannot communicate, it has not been validated in dementia (Reisberg et al., 1982).

when one of the comparisons for Lin et al. was excluded at random.

A further meta-analysis of studies using validated measures of anxiety in dementia was performed, which included 234 participants. Non-pharmacological group interventions were no longer effective at reducing anxiety when studies using non-validated measures of anxiety were excluded from the analysis: the standardised mean difference − 0.31 (CI: −0.66, 0.05), see Appendix D.

7. Non-pharmacological interventions delivered to individuals

Twelve studies investigated non-pharmacological interventions delivered to individuals (see Table 3 for details).

All studies that investigated non-pharmacological interventions delivered to individuals were parallel pilot RCTs or RCTs, total participant numbers ranged from 20 - 128 participants and study duration ranged between 3 - 24 weeks. Three studies focused on people living with Alzheimer's exclusively. A range of instruments was used to measure anxiety, as presented in Table 3. In the meta-analysis, the standardised mean difference was − 0.47 (CI: −0.75, −0.18). I^2 statistic was 68% representing substantial heterogeneity. Results suggested non-pharmacological interventions delivered to individuals were effective in treating anxiety in people living with dementia compared to the control groups (Fig. 8). As was the case with the group interventions, although the studies are small, music therapy appeared effective but other types of intervention types showed mixed results. A sensitivity analysis was performed as more than one comparison was made for Rodriguez-Mansilla et al. and Kolanowski et al. giving them excess weight in the analysis. The results did not differ when one of the comparisons of the respective studies was removed at random.

A further meta-analysis of studies using validated measures of anxiety in dementia was performed, which included five studies with 177 participants (Spector et al., 2015; Stanley et al., 2013; Pu et al., 2020; De Oliveira et al., 2019; Oliveira et al., 2021). This did not alter the results: standardised mean difference − 0.40 (CI: −0.7, −0.1).

7.1. Subgroup analysis according to setting

A planned subgroup analysis was performed according to whether the different types of interventions were aimed at participants living in their own homes or a care home, including residential and nursing homes. Enough studies investigating stimulating cognitive and physical activity interventions and muscular approaches occurred in both settings, therefore these two intervention types were included in the meta-analysis. For the four studies conducted in care homes, the standardised mean difference was – 0.42 (CI: −0.79, −0.06) and for the six studies conducted in people living in their own homes, the standardised mean difference was – 0.44 (CI: −0.65, −0.22). Results show non-pharmacological interventions conducted in these settings were effective in reducing anxiety in people living with dementia, compared to the control groups (Appendix E). The results show studies conducted with participants living in care homes were as effective as studies conducted with people living in their own homes.

8. Discussion

Our results suggest some non-pharmacological interventions are effective in reducing anxiety in people living with dementia, when compared to care as usual or an active control. We found some intervention types appeared more effective than others; music therapy, those that use muscular approaches (e.g., massage) and those that use stimulating cognitive and physical activities (e.g., tailored exercise programmes) were found to be effective, while cognitive approaches (e.g., CBT) and sensory stimulation (such as PARO) were not. A range of pharmacological interventions demonstrated potential effectiveness in single studies, compared to placebo or another medication; including antipsychotics, antidepressants and probiotics. However, meta-analyses were not performed due to study heterogeneity. Many studies were assessed as 'high' risk of bias and we must therefore be cautious of the findings.

Results echo similar findings of depression, that non-

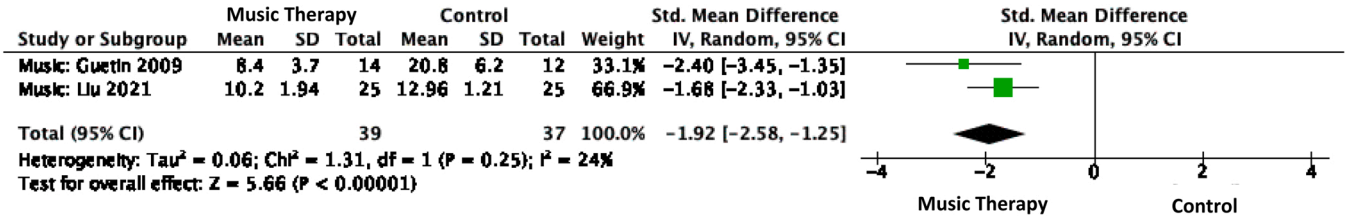

Fig. 2. Meta-analysis of music therapy studies.

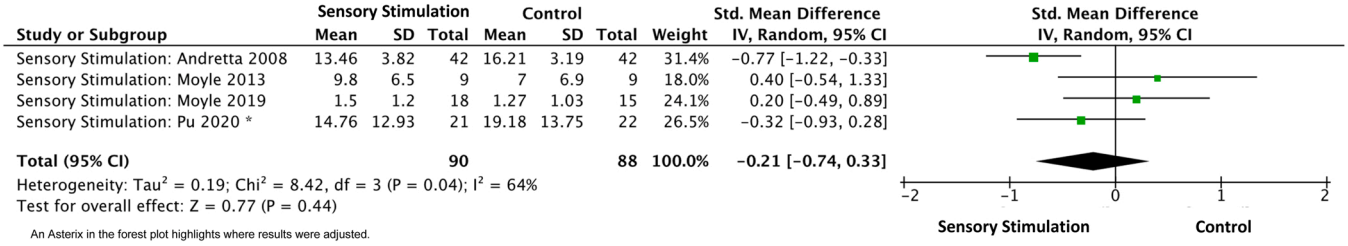

Fig. 3. Meta-analysis of sensory stimulation studies.

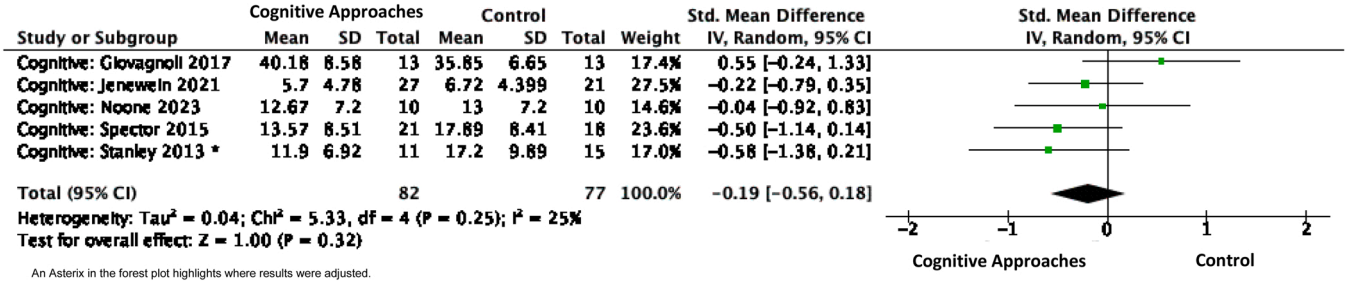

Fig. 4. Meta-analysis of studies that used a cognitive approach.

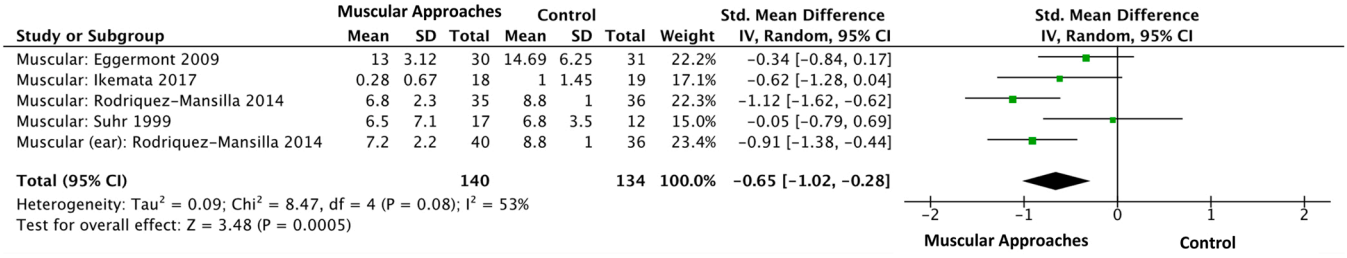

Fig. 5. Meta-analysis of studies that used a muscular approach.

pharmacological interventions including massage and touch therapy are more effective than pharmacological interventions for reducing depression symptoms when compared to usual care (Watt et al., 2021). This is unsurprising, given the substantial overlap in symptoms, aetiology and presentations of anxiety and depression in people with dementia (Seignourel et al., 2008).

We did not meta-analyse findings for supplements/pharmacological interventions due to study heterogeneity. However, there was evidence of potential effectiveness for some including Ginkgo biloba, probiotics, olanzapine, loxapine and citalopram compared to placebo, olanzapine compared to bromazepam, and buspirone and risperidone compared to haloperidol. Medications could therefore be effective, but this needs to be balanced with safety. For example, antipsychotics should be avoided where possible in people living with dementia as there is an increased risk of stroke and other side effects that require monitoring (NICE, 2018a). Antipsychotics may be considered for those with severe agitation or distress who are at risk of harm to themselves and others. However, this should be initiated by a specialist and used alongside other activities. There may be a role for probiotics which have fewer side effects and could provide a safer alternative to medications, such as antipsychotics; especially as there is growing interest in the gut/brain pathway and reviews of the literature suggest their effectiveness in the treatment of depression in non-dementia populations (Nadeem et al., 2019). Further research is needed in this area to determine effectiveness in people living with dementia.

Although participants numbers were small, music therapy was effective in reducing anxiety in dementia. This is supported by findings of a Cochrane Review that investigated music based therapeutic interventions in people living with dementia, which included 13 studies and 478 participants where the standardised mean difference for changes in anxiety was − 0.43 (CI −0.72, −0.14) (Van Der Steen et al., 2018). Our inclusion criteria were different in several ways, for example we only included studies where participants had clinically significant anxiety at the start of the study. Music therapy has also been found to be effective for other distressing symptoms, such as agitation which can present similarly to anxiety in people living with dementia (Seignourel

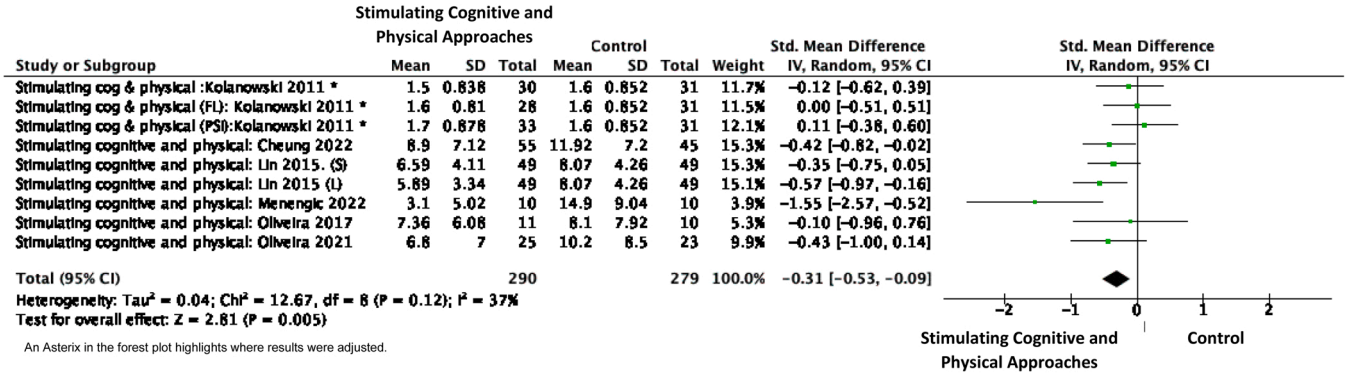

Fig. 6. Meta-analysis of studies that used stimulating cognitive and physical activities.

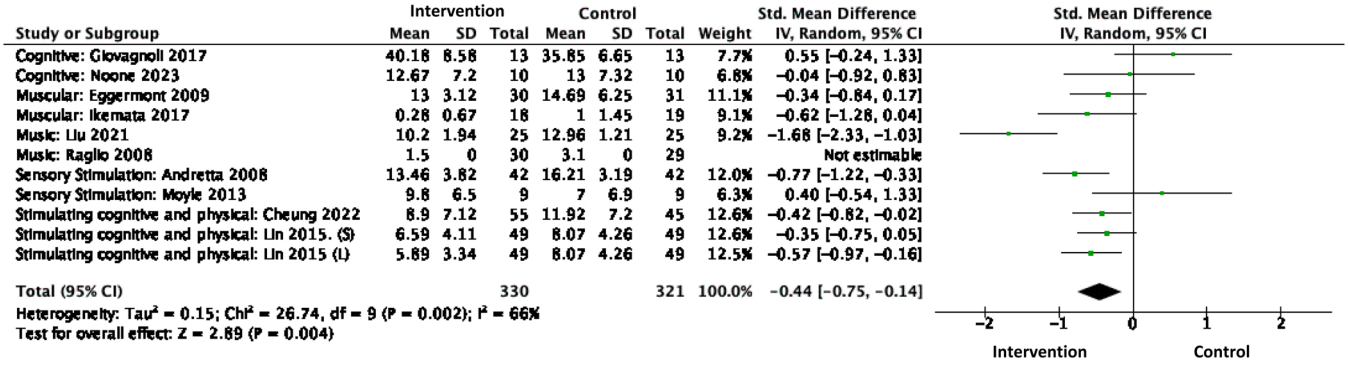

Fig. 7. Meta-analysis results for non-pharmacological group interventions for all included studies.

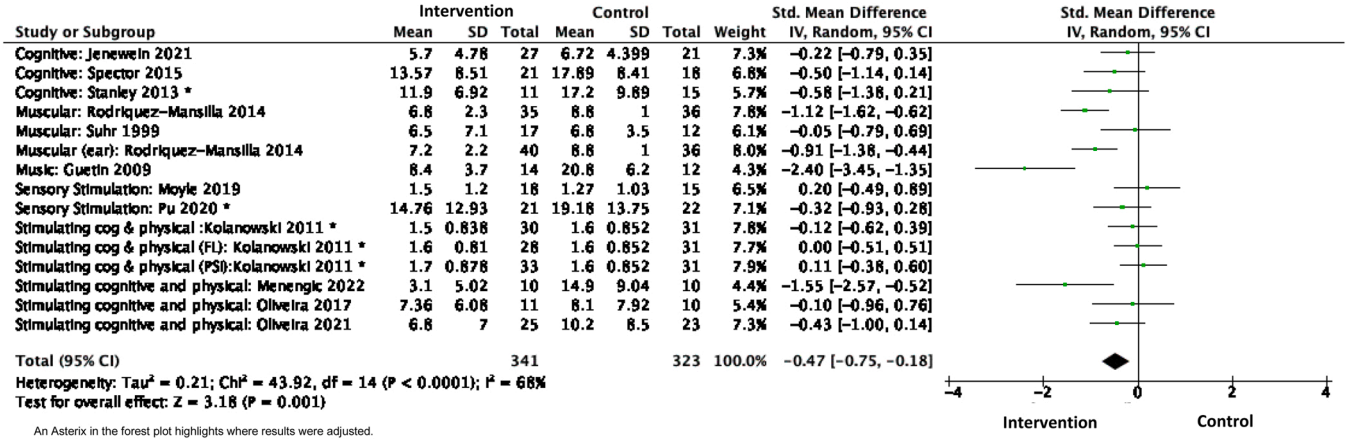

Fig. 8. Meta-analysis results for non-pharmacological interventions aimed at individuals.

et al., 2008). A systematic review led by a member of our team found that for care home residents living with dementia, music therapy was effective for emergent agitation and decreasing symptomatic agitation (Livingston et al., 2013). Our results therefore support a growing evidence base that indicate music therapy is effective in treating anxiety (and other similar symptoms) in dementia.

Interventions using muscular approaches were also found to be effective, although this is not supported by all previous studies in the area (Wu et al., 2017). A previous systematic review and meta-analysis that used a narrower definition of 'muscular approaches' found massage and touch therapy were not effective in reducing anxiety, SMD − 0.63 (CI −1.63, 0.36) (Wu et al., 2017). More research is therefore needed in this area.

We found interventions using cognitive approaches and cognitive stimulation were not effective, as supported by recent Cochrane Reviews. One explored psychological treatments for depression and anxiety in dementia and mild cognitive impairment (Orgeta et al., 2022). The authors included three studies with 143 participants and the standardised mean difference was − 0.03 (CI: −0.36, 0.30). This review differed to ours as it included mild cognitive impairment. The other explored cognitive stimulation to improve cognitive function in dementia and included six studies and 410 participants (Woods et al., 2023). Overall, cognitive stimulation was not effective in reducing anxiety, the standardised mean difference 0.11 (CI −0.09, 0.30).

8.1. Strengths and limitations

Strengths of this review include a comprehensive literature search aided by an information scientist and conducted according to published guidelines (Page et al., 2021). There was also substantial agreement between reviewers, and a broad multidisciplinary team was involved in the interpretation of results, including primary care physicians, social care experts and a psychiatrist. There are however limitations to acknowledge. Limitations of some of the studies include small sample sizes and heterogeneity among studies, which makes the effect size estimates hard to interpret, for example, when comparing non-pharmacological interventions delivered to individuals and groups. For some studies (such as Kolowanski et al., 2011) we included multiple comparisons in the meta-analysis, which would have increased their weighting, we must therefore be cautious of the results. However, to remedy this sensitivity analyses were performed excluding comparisons at random when more than one was present, and there was very little change in the results when this was done. Also, we were unable to report on specific dementia subtypes or severity, which may have identified different efficacy of treatments in sub-populations.

Many studies used instruments where anxiety was observed in participants, that is, anxiety was not self-reported, which may have influenced results and contribute to observer bias. However, it should also be acknowledged that some people living with dementia may not have capacity to self-report and in these cases observations are reasonable and to be expected. Also, the studies occurred in countries around the world, with different population characteristics and health systems, meaning direct comparisons may not be appropriate. It may also not be appropriate to compare results of studies conducted many years ago (for example, in the 1980 s) when dementia care was very different to current times. Only three studies aimed to investigate improvements of anxiety exclusively and many targeted broader BPSD, it is therefore possible that reductions in anxiety could be due to reductions in other BPSD, for example hallucinations. Only 17 out of 31 studies used anxiety measures that have been validated in dementia populations, which was a main reason why many studies were downgraded in relation to the quality assessment. Some of the measures were validated in older populations, eg BAI, and others validated in primary care, eg GAD-7. When all studies were included in the meta-analysis, regardless of if they were validated in dementia or not, both non-pharmacological group and interventions aimed at individuals were effective.

8.2. Implications for policy, practice and research

Our results have practice and commissioning implications and could lead to the development and use of more non-pharmacological interventions to help reduce anxiety among people living with dementia in the community, including non-pharmacological interventions such as music therapy. Results therefore have the potential to be added to current and future guidelines on the treatment of anxiety in people living with dementia. Other distressing symptoms, such as depression, receive wider coverage in research than anxiety, despite the prevalence of anxiety being high in this population, with adverse outcomes. More research is therefore needed focusing on anxiety, where it is the main outcome of the study and dementia validated measures should be used. There is a lack of data covering socioeconomic groups, ethnicity, and cost; and future studies should report on these factors. Over half of the studies included participants with any type of dementia and future studies could investigate if there are differences in effectiveness depending on dementia subtype. A single study of probiotics demonstrated potential effectiveness. Considering growing interest in the gut/brain pathway as a point of intervention in anxiety and depression, this may be a fruitful avenue for future research. Finally, results suggest music therapy is effective but the sample sizes were small, further studies should therefore be conducted to provide further evidence and explore why this type of therapy is effective.

9. Conclusion

Results suggest some non-pharmacological interventions are effective in reducing anxiety in community-dwelling people living with dementia, including music therapy, muscular approaches and stimulating cognitive and physical activities. However, further research is needed due to small sample sizes, heterogeneity and a lack of use of validated measures. There was limited evidence on pharmacological interventions, with single studies of a range of medications. For most of the pharmacological interventions for which evidence of efficacy was found, side effect profiles significantly curtail use in practice.

Declaration of Competing Interest

There are no competing interests to declare.

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Appendix A. Example search strategy in Medline

Dementia	
1	exp dementia/
2	exp alzheimer disease/
3	exp dementia, vascular/
4	exp dementia, multi-infarct/
5	exp frontotemporal lobar degeneration/
6	exp Frontotemporal Dementia/
7	exp lewy body disease/
8	or exp lewy body/
9	Dementia.mp.
10	alzheimer* .mp.
11	vascular dementia.mp.
12	multi-infarct dementia.mp.
13	frontotemporal dementia.mp.
14	frontotemporal lobar degeneration.mp.
15	(lewy adj5 bod* adj5 disease).mp
16	OR 1-15
Anxiety	
17	exp mood disorders/
18	exp neurotic disorders/
19	exp Anxiety/
20	exp panic disorder/
21	exp agoraphobia /
22	exp anxiety disorders/
23	mood disorder* .mp.
24	neurotic disorder.mp.
25	Anxiety.mp.
26	anxiety disorder.mp.
27	Agoraphobia.mp.
28	panic disorder.mp.
29	OR 17-28
30	exp Randomized Controlled Trials as Topic/
31	exp Controlled Clinical Trial/
32	exp Clinical Trial/
33	randomi?ed controlled trial.pt.
34	controlled clinical trial.pt.
35	random$.ti,ab.
36	(control$ adj2 (trial? or study or studies)).ti,ab.
37	double-blind method/ or random allocation/ or single-blind method/
38	((double or single or triple or treble) adj2 blind$).ti,ab.
39	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	exp animals/ not humans.sh.
41	39 not 40
42	16 and 29 and 41

Appendix B. : Quality assessment

	D1	D2	D3	D4	D5	Overall
Ikemata et al						
Jenewein et al						
Pu et al						
Rodríguez-Mansilla et al						
Moretti et al						
Barnes et al						
Nacu et al						
Leonpacher et al						
Cantillon et al						
Moyle et al (2019)						
Giovagnoli et al						
Spector et al (2015)						
Suhr et al						
Guétin et al						
Lin et al						
Mintzer et al						
Suh et al						
Oliveira et al (2017)						
Oliveira et al (2021)						
Liu et al						
Stanley et al						
Moyle et al (2013)						
Raglio et al						
Scripnikov et al						
Andretta et al						
Kolanowski et al						
Eggermont et al						
Noone et al						
Cheung et al						
Menergic et al						
Akhgarjand 2022						

Domains

D1= Bias arising from the randomisation process

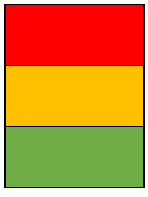
D2= Bias due to deviations from intended interventions

D3= Bias due to missing outcome data

D4= Bias in measurement of the outcome

D5= Bias in the selection of the reported result

Judgement:



High concern

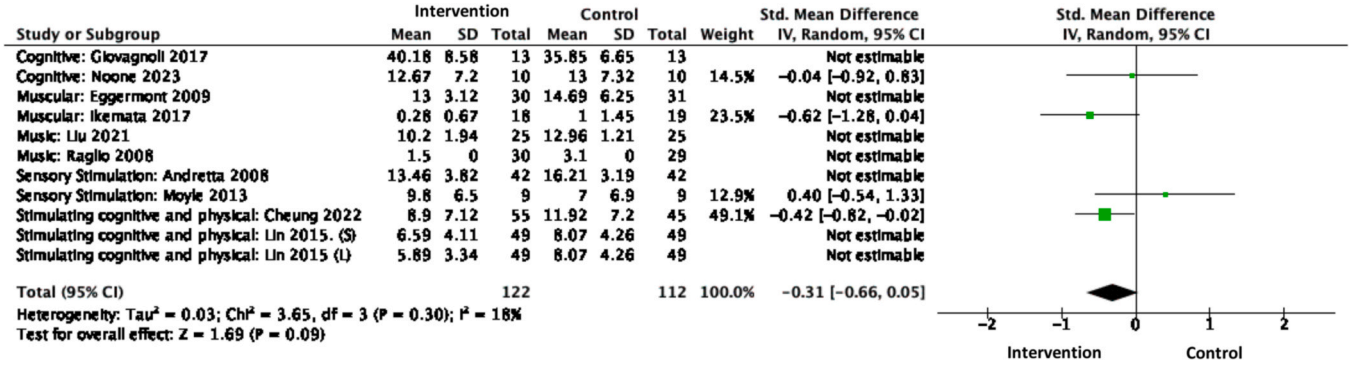
Some concern

Low concern

Appendix C. : GRADE Assessment

Quality assessment							No of patients		Effect		Quality of Evidence for OH	Recommendation
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	95% CI	SMD		
Non-pharmacological group interventions												
10	RCT	Half information is from studies at high ROB	Yes- heterogeneity is 66% and point estimates vary	No	No	downgraded due to high risk of bias, inconsistency and small studies.	330	321	-0.75, − 0.14	–0.44	Low	Effective in reducing anxiety compared to the control group but there was high heterogeneity. Many studies used measures not validated in dementia and small sample sizes were used. Validated measures should be used in future studies that focus specifically on anxiety, instead of general BPSD.
Non-pharmacological interventions aimed at individuals												
12	RCT	Half information is from studies at high ROB	Yes- heterogeneity is 68%	No	No	downgraded due to high risk of bias, inconsistency and small studies.	341	323	-0.75, − 0.18	-0.47	Low	Effective in reducing anxiety compared to the control group but there was high heterogeneity. Many studies used measures not validated in dementia and small sample sizes were used. Validated measures should be used in future studies that focus specifically on anxiety, instead of general BPSD.
Supplements & Pharmacological interventions												
9	RCT	Half information is from studies at high ROB	Unable to perform a meta-analysis. Two studies did not report between group differences, the other seven studies showed significant differences between groups	No	No	downgraded due to high risk of bias	751	682	N/A	N/A	Low	These interventions are potentially effective in reducing anxiety compared to the control group but a meta-analysis could not be performed. Many studies used measures not validated in dementia. Validated measures should be used in future studies that focus specifically on anxiety, instead of general BPSD.

Appendix D. : Studies included that used validated measures of anxiety in dementia



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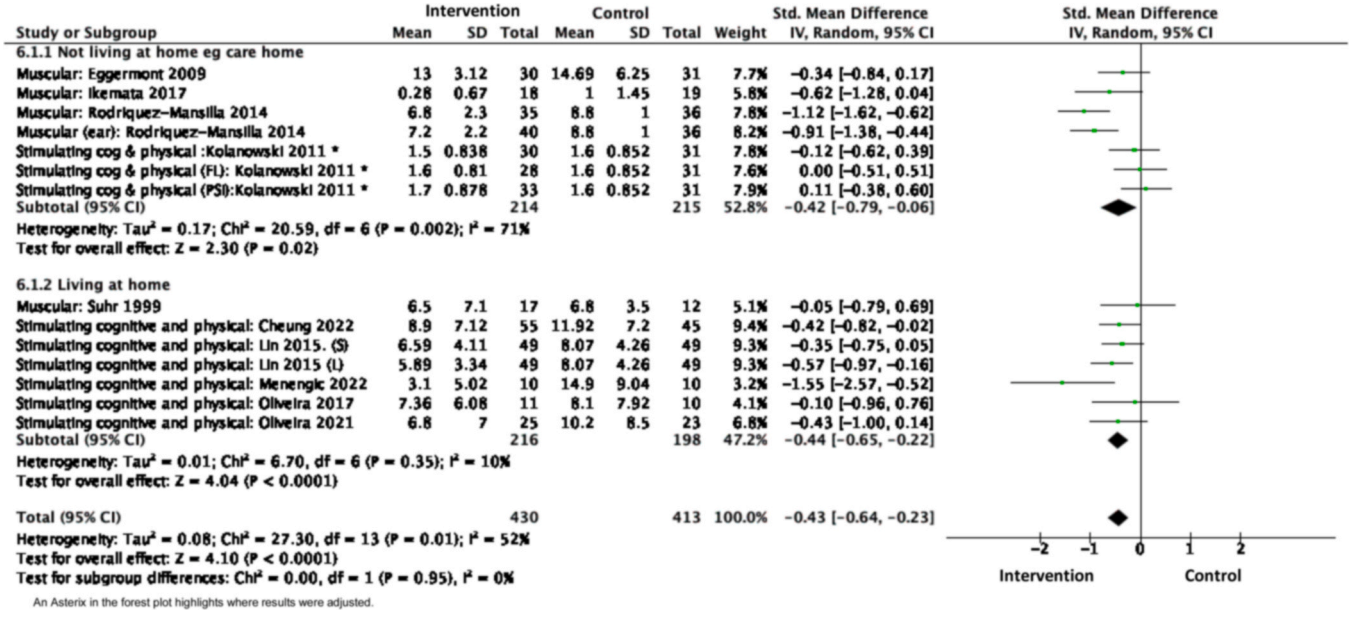
Appendix E. : Sub-group analysis showing results according to setting



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