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Manual massage for persons living with dementia: A systematic review and meta-analysis

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ABSTRACT

Background: The number of persons living with dementia will increase. So far, pharmacological management is limited because of small effect sizes and side effects of the drugs. Therefore, it is important to assess non-pharmacological treatment options such as massage, which have nearly no side effects and are easy for caregivers to apply.
Objectives: To conduct a systematic review with meta-analysis, aiming to pool the evidence for the efficacy of manual massage for persons living with dementia.
Design: A systematic review and meta-analysis.
Data sources: EMBASE, Medline, PubMed, PSYinfo, BIOSIS, EBM, PSYCINDEX, Osteopathic Research Web, and OSTMED.DR were searched, regardless of publication year, through August 2017.
Review methods: Randomized controlled trials (RCTs) evaluating manual massage in patients with dementia with or without using (aromatic) oil were included. The intervention of the control group had to guarantee no physical contact between caregiver and patient. Only studies assessing behavioural and psychological symptoms of dementia, cognitive abilities or depressive symptoms with validated instruments were included. Two reviewers independently extracted data and assessed risk of bias using The Cochrane Collaboration's 'Risk of bias' tool. Continuous outcomes are given as standardized mean difference (SMD), with 95% confidence intervals (CI) if different scaling of outcome measurement was used, and as mean difference (MD), with 95% confidence intervals (CI) for identical scaling. Data were pooled using the random-effects model. Sensitivity analysis considered type of massage, oil and outcome. Funnel plots were performed.
Results: Eleven RCTs, with a total of 825 persons living with dementia, were eligible for qualitative synthesis and nine for quantitative synthesis. Two studies, with a total of 95 participants, had a high risk of bias. A pooled analysis of the mean change showed a benefit of manual massage compared to the control group using the Cohen Mansfield Agitation Inventory (SMD = –0.56, 95% CI [–0.95, –0.17], P = 0.005), which included six studies with 395 participants, and using the Cornell Scale of Depression in Dementia (MD = –6.14 [–8.66, –3.61], P < 0.00001), which included three studies with 193 participants. No significant effect could be demonstrated using the Neuropsychiatric Inventory and Mini Mental State Examination. Subgroup analysis of 'acupressure' did not show significant group differences.
Conclusions: Manual massage may serve as a non-pharmacological strategy to improve behavioural and psychological symptoms in persons living with dementia. Thus, healthcare professionals and family caregivers should be encouraged to apply massage to their patients and relatives. More research is needed, however, to provide clearer recommendations with respect to frequency and types of massage.

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What is already known about the topic?

- Previous studies suggest a positive effect of manual massage on persons living with dementia with regard to behavioural and psychological symptoms.
- Clear recommendations regarding massage technique, the use of aroma oils and frequency are lacking

What this paper adds

- This study shows a significant improvement in behavioural and psychological symptoms following manual massage in persons living with dementia
- Subgroup analyses show improved outcomes following the use of aroma oil and in massage types without acupressure.

1. Introduction

1.1. Background

The complexity and variability of dementia is indicated within the definition of dementia from the World Health Organization (Dias et al., 2006). Dementia is not described as a disease but more as a syndrome, distinguished through disturbances *of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement* (Dias et al., 2006). This complexity should be considered by nurses and physicians treating and caring for persons living with dementia. Cognitive disturbances are accompanied by behavioural and psychological symptoms in 90% of dementia patients (Azermai, 2015) and occur in the form of depression, apathy, and anxiety (Anand et al., 2017). Other symptoms include agitation, hallucinations, and alterations of sleep and appetite. These symptoms reduce the quality of life and the ability of persons living with dementia to function socially (Azermai, 2015; Cheng, 2017). It is especially stressful for family caregivers. Therefore, self-management strategies led by the carers in order to positively influence the patients' mood and behaviour changes are important in the context of the patients' daily lives. Nurses play a central role not only in the care of dementia patients but also in the self-management support of patients and their family care givers (Huis in het Veld et al., 2016).

Due to the aging population, degenerative disorders like dementia will become more prevalent in the future. According to the World Alzheimer Report 2016, nearly 50 million people worldwide suffer from dementia (Prince et al., 2016). That number is expected to rise to about 75 million in 2030 and more than 130 million in 2050. Based on current evidence, the effects of pharmacological treatment of cognitive and psychological-behavioural symptoms in persons living with dementia are very limited (Dyer et al., 2017; Masopust et al., 2018). They predominantly target the cognitive function but not the neuropsychiatric symptoms (Blanco-Silvente et al., 2017; Tricco et al., 2017). Cholinesterase inhibitors entail many side effects, such as headache, diarrhoea, nausea, and vomiting (Renn et al., 2018). Furthermore, antipsychotic drugs often cause dysphagia, extrapyramidal symptoms and sedation, and lead to higher mortality in persons living with dementia (Masopust et al., 2018). Thus, non-pharmacological treatments, are regarded as important alternatives and recommended as first-line treatments in dementia guidelines (Azermai et al., 2012). Indeed, guidelines (National Institute for Health and Clinical Excellence, 2006) and systematic reviews (Masopust et al., 2018; Wu et al., 2017) emphasize the importance of these strategies in reducing behavioural and psychological symptoms in dementia.

Manual massage using mainly the hands affects the skin and, depending on the location and the applied pressure, vascular, muscular, and nervous systems (Fellowes et al., 2004). It can be applied as rubbing, stroking, or pressing on different parts of the body, such as the hands, feet, or back (Viggo Hansen et al., 2006). The importance of being touched begins with the first breath (Moore et al., 2012). Moore et al. (2012) demonstrated in their review that skin-to-skin contact between mother and newborn infants appears to benefit breast feeding outcomes, promote cardio-respiratory stability, and decrease infant crying. The binding hormone oxytocin seems to play an important role for parent-infant relationship (Vittner et al., 2018). Studies have also shown that oxytocin leads to an improvement of cognition and behavioural symptoms in people with Frontotemporal Dementia (Jesso et al., 2011; Tampi et al., 2017). Walker et al. (2017) found that being touched activates a particular sub-class of unmyelinated C-fibre afferents. These fibres stimulate magnocellular neurones of the paraventricular and supraoptic nuclei of the hypothalamus (Stoop, 2014) and trigger the release of oxytocin in the posterior pituitary. Within the vascular system, oxytocin exerts numerous peripheral effects (Yang et al., 2013) and contributes, through widely distributed oxytocin receptors throughout the central nervous system, to a range of sensory and psychological processes essential for adaptive social behaviour (Mitre et al., 2016; Walker et al., 2017).

The efficacy of massage for behavioural and psychological symptoms of dementia has been investigated in numerous recent studies (Kwan et al., 2017; Rodriguez-Mansilla et al., 2015; Yang et al., 2016a), but the strength of the recommendation in guidelines for dementia remains weak (German Society of Psychiatry, Psychotherapy and Neurology, German Society of Neurology, 2016; Canadian Consensus Conference, 2007; National Institute for Health and Clinical Excellence, 2006).

Three systematic reviews have investigated the effect of massage on persons living with dementia (Livingston et al., 2014; Viggo Hansen et al., 2006; Wu et al., 2017). Viggo Hansen et al. (2006) included only two studies and could not derive specific recommendations because of a lack of evidence. 13 studies focusing on sensory interventions were included in the systematic review by Livingston et al. (2014). Seven of them were randomised controlled trials and demonstrated significant improvements of agitation for acupressure, massage and 'snoezelen' (a type of multisensory intervention involving tactile, light and auditory stimulation). However, the level of evidence the studies provided was limited. Wu et al. (2017) included 11 studies and was the first meta-analysis; it revealed significant improvement of behavioural and psychological symptoms of dementia in total and subgroup scores. However, Wu et al. (2017) included studies evaluating interventions, which did not touch the skin ('therapeutic touch') and studies with only one treatment session.

Therefore, when considering the oxytocin hypothesis, only studies of a physical contact between care-giver and care-receiver should be included and treatment duration should be adequately considered.

1.2. Objectives

To conduct a systematic review with meta-analysis of the evidence for the efficacy of manual massage for persons living with dementia.

2. Methods

2.1. Protocol and registration

A study protocol was registered at PROSPERO (CRD42017074124).

2.2. Eligibility criteria

We included randomized controlled trials (RCTs) evaluating skin-to-skin contact, hand massage interventions for persons living with dementia.

Studies involving patients with any type of dementia according to diagnostic criteria were included. In the primary studies, the following were accepted as diagnostic criteria: Mini Mental State Examination, Diagnostic and Statistical Manual of Mental Disorders IV, diagnosis made by a physician, or documented diagnosis of dementia.

Interventions were included if caregivers exerted physical contact on a patient by using their hands and with a therapeutic intention. Interventions without a mechanical stimulus on the skin were excluded. The intervention could affect any part of the body, but the skin barrier could not be broken, so needle techniques such as acupuncture were also excluded. Furthermore, the strength of the pressure could range from soft effleurage techniques during a massage or an osteopathic positional release technique to hard acupressure within the limits of the patient's pain threshold. Combined interventions with a specific ethereal oil, such as lavender, or a pharmaceutical application on the skin, such as a patch, were also included. Studies with an intervention duration of less than one week were excluded.

Studies were excluded in which there was physical contact between caregiver and care receiver in the control group.

The differences in mean change of behavioural and psychological symptoms, cognitive deficits and daily living activities were assessed as primary outcomes using the following standardized measurements: Mini Mental State Examination, Cohen Mansfield Agitation Inventory, Neuropsychiatric Inventory, Cornell Scale of Depression in Dementia, and Barthel Index. Studies were included if they considered at least one of the aforementioned outcomes.

Language was restricted to English or German.

2.3. Information sources

To guarantee transparency and appropriate structure of the article, the authors utilised the PRISMA Guideline (Moher et al., 2009) and the Cochrane Handbook (Higgins, 2011).

A systematic literature search was conducted in August 2017. The search strategy for identifying RCTs included the following main databases: EMBASE, Medline, PubMed, EBM, PSYCinfo, BIOSIS, PSYNDEX, and two specific databases for the field of osteopathy, Osteopathic Research Web and OSTMED.DR.

2.4. Search

The following search terms based on the Medical Subject Headings indices for "dementia" and "musculoskeletal manipulations", appearing under "complementary therapies", were used: musculoskeletal manipulations, musculoskeletal, manual therap*, manipulative medicine, manipulative, chiropractic, chiropractic manipulation, chiropractic practice, chiropractic, osteopathic manipulation, osteopathic, osteopathic medicine, craniosacral therapy, craniosacral, cranio sacral, soft tissue therapy, soft tissue therap*, acupressure, and massage combined with dementia, dement*, alzheimer disease, alzheimer*, and lewy body. See Appendix 1 for the precise search strategy.

For Osteopathic Research Web and OSTMED.DR, the terms were combined separately. Reference lists of review articles and of all included studies were assessed to find other potentially eligible studies.

2.5. Study selection

The search strategy detailed above was used to obtain titles and abstracts of studies with possible relevance for the review.

One review author (FM) screened the titles and abstracts. Two review authors (FM, CK) read the full texts of the remaining articles. A third review author (SJ) aided this process and provided the third vote to help resolve disagreements.

2.6. Data collection

One review author (FM) extracted data. Information about the country, setting, population, patients' inclusion criteria, intervention and control of the included studies was extracted. Additionally, information about intervention data including type, technique, frequency and duration of the intervention-period was obtained. To establish the duration of the intervention a table was created, including intervention in weeks, sessions per day, frequency per week, and session length; the total physical contact duration was then calculated. In order to maintain consistency with respect to the treatment duration, the post-baseline values were extracted within an intervention period of between two to five weeks. For example, in a study which provided post-baseline values for both five and eight weeks, only the five week values were considered for the analysis.

In case there were more publications of one trial, only the publication with the most complete data set was used. The study authors were contacted for clarification if there were unclear or missing data. Such data were also excluded from the meta-analysis and if missing data rendered the result uninterpretable then it was clearly stated.

2.7. Risk of bias in individual studies

Risk of bias of the included studies was assessed independently by two review authors (FM, CK) using The Cochrane Collaboration's 'Risk of bias' tool (Higgins, 2011). One review author (FM) collated the results. Discrepancies were discussed until a consensus was reached.

2.8. Summary measures

The effect of manual massage on the Cohen Mansfield Agitation Inventory, Neuropsychiatric Inventory, Cornell Scale of Depression in Dementia, Mini Mental State Examination, and Barthel Index were deemed primary outcomes; all were measured with continuous data. The Mean difference (MD) was chosen as an effect measure when the pooled studies used the identical scaling of outcome measurement and the standardized mean difference (SMD) was used in the case of different scaling. These two effect measures were given with 95% confidence intervals (CIs). A significance level of ≤ 0.05 was adopted.

2.9. Synthesis of results

Data was pooled using the random-effects model. Statistical heterogeneity was assessed with the standard chi-square and I^2. ReviewManager 5.3 (The Cochrane Collaboration, 2014) was used.

2.10. Unit of analysis issues

In trials with more than two intervention groups, only the relevant intervention groups were included as pair-wise comparisons with the control group (i.e. those without physical contact). For estimating the SD of the mean change, a two-step procedure was performed. If possible, the correlation (*rho*) of the mean change was calculated. Otherwise, a correlation of 0.5 was assumed. For the SD, the formula $SD^N = \sqrt{[(SD^{t0})^2 + (SD^{t1})^2 + rho * SD^{t0} * SD^{t1}]}$ was used.

2.11. Risk of bias across studies

For reporting bias, the included RCTs were compared with available protocols. Funnel plots were performed with respect to outcome and checked for asymmetry. For the generation of a funnel plot, the minimum number of eligible studies per outcome measure was 10 (Sterne et al., 2011).

2.12. Additional analyses

Subgroup analyses were performed with respect to intervention type, outcome measure, oil usage, and treatment duration.

The influence of study quality and sample size was checked by sensitivity analysis of the pooled data. It was performed when a study had three or more low risk items in the 'Risk of bias' tool (Higgins, 2011).

3. Results

3.1. Study selection

The electronic search strategy identified 1661 studies. After title/abstract screening, 32 studies remained. Eleven RCTs met all inclusion criteria. The flow chart in Fig. 1 displays percentages of the databases and exclusion criteria during full text analysis. In full-text analysis, we excluded 21 studies. For eight studies, the design did not meet the inclusion criteria. In two studies, diagnosis of dementia as defined in this paper was not obligatory for inclusion. For four studies, intervention duration did not meet inclusion criteria. Two studies investigated divergent intervention techniques (doll therapy and energy flow). Both interventions did not fulfil physical contact between caregiver and care receiver. In one study there was a lack of clarity as to whether physical contact

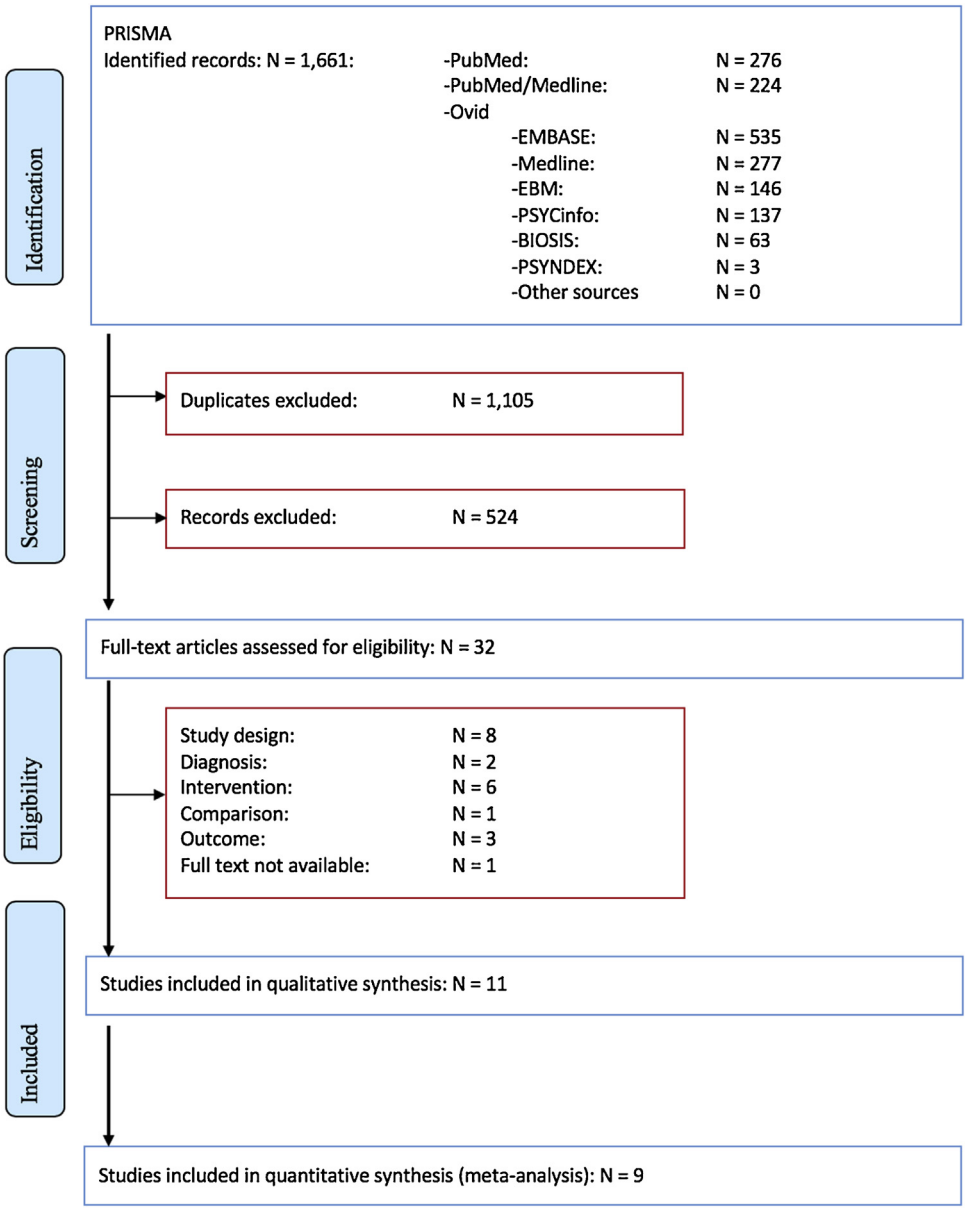

Fig. 1. PRISMA Flow Chart.

did not occur in the control group. Another study measured change by non-standardized video analysis. One investigated pain and another only biological parameters. One full text was not made available despite the author being contacted directly.

3.2. Study characteristics

Eleven RCTs, with a total of 825 persons living with dementia, were included. Three studies were performed in Taiwan (Yang et al., 2015; Yang et al., 2016a,2016b), three in Japan (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013), two in Australia (Fu et al., 2013; Moyle et al., 2014), and one each in Turkey (Turten Kaymaz and Ozdemir, 2017), Spain (Rodriguez-Mansilla et al., 2015) and China (Kwan et al., 2017). Four studies recruited their participants from hospitals (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013; Turten Kaymaz and Ozdemir, 2017), another four from long-term care facilities (Fu et al., 2013; Moyle et al., 2014; Yang et al., 2016a, 2016b), two from residential care homes (Kwan et al., 2017; Rodriguez-Mansilla et al., 2015), and one from long-term care facilities and residential care homes (Yang et al., 2015).

In six studies dementia was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders IV (Fu et al., 2013; Kudoh et al., 2009; Mariko et al., 2015; Rodriguez-Mansilla et al., 2015; Satoh et al., 2013; Yang et al., 2015), two according to Mini Mental State Examination (Yang et al., 2016a, 2016b), two mainly according to documents reporting dementia (Kwan et al., 2017; Moyle et al., 2014), and one according to a diagnosis made by a physician (Turten Kaymaz and Ozdemir, 2017).

Four studies investigated aroma massage (Fu et al., 2013; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2016a, 2016b), one investigated aroma acupressure (Yang et al., 2015), two investigated massage therapy (Kudoh et al., 2009; Moyle et al., 2014), two investigated acupressure (Kwan et al., 2017; Mariko et al., 2015), one investigated acupressure in combination with rivastigmine patch (Satoh et al., 2013), and one investigated a massage therapy and acupressure intervention group (Rodriguez-Mansilla et al., 2015). Two studies applied massage on the hands (Fu et al., 2013; Turten Kaymaz and Ozdemir, 2017), two on the feet (Kudoh et al., 2009; Moyle et al., 2014), one on the lower limbs and back (Rodriguez-Mansilla et al., 2015), and one on the shoulders, arms, and neck of the patients (Yang et al., 2016a). One study did not describe localization of massage application (Yang et al., 2016b). In 10 comparison groups non-physical contact was guaranteed, with three having no intervention (Rodriguez-Mansilla et al., 2015; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2016b), three having placebos (Fu et al., 2013; Mariko et al., 2015; Moyle et al., 2014), two having routine care (Yang et al., 2015, 2016a), and two having another intervention (Kwan et al., 2017; Satoh et al., 2013). One study did not provide information (Kudoh et al., 2009).

Agitation was measured in seven studies using the Cohen Mansfield Agitation Inventory (Fu et al., 2013; Kwan et al., 2017; Moyle et al., 2014; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2015, 2016a, 2016b) and in four using the Neuropsychiatric Inventory (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013; Turten Kaymaz and Ozdemir, 2017). Four studies investigated cognitive deficits using Mini Mental State Examination (Fu et al., 2013; Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013). Three studies each measured depressive symptoms using the Cornell Scale of Depression in Dementia (Rodriguez-Mansilla et al., 2015; Yang et al., 2016a, 2016b) and activities of daily living through the Barthel Index (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013). Further rare outcomes were pain and biological indicators (Kwan et al., 2017; Rodriguez-Mansilla et al., 2015; Yang et al., 2015).

Table S1 summarises the inclusion criteria and population, interventions and comparisons, outcome measures, and setting. Table 1 summarises the results of the included studies.

Four studies used an intervention duration of four weeks (Kudoh et al., 2009; Mariko et al., 2015; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2015), two of eight weeks (Yang et al., 2016a, 2016b), and one each of two (Kwan et al., 2017), three (Moyle et al., 2014), six (Fu et al., 2013), and 12 weeks (Rodriguez-Mansilla et al., 2015). Seven studies applied their intervention once a day (Kudoh et al., 2009; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2015, 2016a, 2016b) and three twice a day (Fu et al., 2013; Kwan et al., 2017; Mariko et al., 2015). Frequency per week was five times in five studies (Kudoh et al., 2009; Kwan et al., 2017; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015; Yang et al., 2015), three times in one study (Turten Kaymaz and Ozdemir, 2017), seven times in two studies (Fu et al., 2013; Mariko et al., 2015), and once in two studies (Yang et al., 2016a, 2016b). One study did not provide information about intervention duration, sessions per day, and frequency per week (Satoh et al., 2013). Session length ranged from 10 to 30 min. Two studies did not describe precise duration of one session (Mariko et al., 2015; Satoh et al., 2013). In Kudoh et al. (2009) information about session length was not given. Appendix 2 provides an overview of the frequency and duration of the interventions under evaluation in each study, including a calculation of the total physical contact time in the study. Based on this calculation, the mean physical contact time across all studies was about 265 min. Because of missing data, three studies were omitted from this computation (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013).

3.3. Risk of bias within studies

The overall risk of bias in the included studies was mixed, largely due to missing information and difficulties with respect to blinding of participants and evaluators. Three studies demonstrated low risk of bias (Kwan et al., 2017; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015). Appendix 3 shows the detailed results of risk of bias assessment.

3.3.1. Allocation (selection bias)

Seven studies ensured adequate random sequence generation by using randomized block technique (Kwan et al., 2017; Moyle et al., 2014; Yang et al., 2016a, 2016b), random number table (Fu et al., 2013; Kudoh et al., 2009), or computer random number generator (Rodriguez-Mansilla et al., 2015). Three studies did not provide enough information to judge (Mariko et al., 2015; Satoh et al., 2013; Yang et al., 2015). The study of Turten Kaymaz and Ozdemir (2017) had a high risk of bias by stratifying patients according to their dementia phase and intake of antipsychotic medication.

Five studies (Fu et al., 2013; Kwan et al., 2017; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015; Yang et al., 2015) adequately concealed allocation. Four used an independent and blinded person (Fu et al., 2013; Kwan et al., 2017; Rodriguez-Mansilla et al., 2015; Yang et al., 2015) and one a computer program (Moyle et al., 2014).

3.3.2. Blinding (performance bias and detection bias)

In most studies, blinding of participants and evaluators was unclear (Fu et al., 2013; Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013; Yang et al., 2015; Yang et al., 2016a, 2016b). Three studies blinded participants (Kwan et al., 2017; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015), and two of those also blinded staff (Kwan et al., 2017; Moyle et al., 2014). A performance bias could be observed in Turten Kaymaz and Ozdemir (2017) because a convenient time to treat was suggested by caregivers. Seven studies guaranteed blinding of outcome assessment by using a blinded assessor (Kudoh et al., 2009; Kwan et al., 2017; Mariko

Table 1
Summary of results of included studies.

Author/year	Measurement (outcome)	Results
Turten Kaymaz and Ozdemir (2017)	1) CMAI (BPSD) 2) NPI (BPSD) 3) Zarit Burden Interview (caregivers' burden)	*1) CMAI:* median CMAI scores at 2 and 4 weeks were significantly lower than at baseline ($P < 0.05$) at 4 weeks, the median CMAI score was significantly lower I than in the C ($P < 0.05$) median CMAI score decrease of 36% in I versus 2% in C at 4 weeks *2) NPI:* median NPI scores in I at 2 and 4 weeks were significantly lower than at baseline ($P < 0.05$) median NPI scores in I at 2 and 4 weeks were significantly lower than those in C ($P < 0.05$) median NPI score decrease of 83.3% in I versus increase of 13.6% in C at 4 weeks ($P < 0.05$) NPI scores measuring caregiver distress were significantly lower at 2 and 4 weeks than at baseline ($P < 0.05$), and were significantly lower in I than in C ($P < 0.05$) *3) Zarit Burden Interview:* median Zarit Burden Interview score at 4 weeks was significantly lower in I than in C ($P < 0.05$)
Kwan et al. (2017)	1) CMAI (BPSD) 2) Salivary cortisol	*1) CMAI:* no significance in agitation over time was regarded between I and C ($P = 0.052$) post hoc pairwise tests in the acupressure group showed significant reduction of agitation at T2 (5 weeks) ($P < 0.001$) *2) Salivary cortisol:* significant interaction between groups and time points were observed on the level of salivary cortisol ($P = 0.022$)
Yang et al. (2016a)	1) CMAI (BPSD) 2) CSDD (depression)	*1) CMAI:* no significance regarding over time agitation ($P = 0.316$) significant changes in four specific agitated behaviours: decreased *grabbing onto people or things inappropriately* ($P = 0.01$), decreased *eating or drinking inappropriate substances* ($P = 0.048$), increased *making strange noises* ($P = 0.031$), increased *negativism* ($P = 0.031$) *2) CSDD:* significant decreasing of depressive symptoms over time for I compared to C ($P < 0.001$) five subscales on the CSDD: improvement of *mood-related signs* ($P = 0.001$), *behavioural disturbances* ($P < 0.001$), *physical signs* ($P < 0.001$) and *cyclic functions* ($P = 0.002$); no significant change for *ideational disturbances* ($P = 0.375$)
Yang et al. (2016b)	1) CMAI (BPSD) 2) CSDD (depression)	*1 und 2) CMAI und CSDD:* significant differences in the effects on agitation and depressive symptoms among 3 I's ($P < 0.01$) post hoc analysis showed that aroma-massage therapy was more effective than reminiscence therapy and cognitive stimulating therapy in improving agitated behaviours ($P < 0.001$), and in alleviating depressive symptoms, too ($P < 0.001$)
Yang et al. (2015)	1) CMAI (BPSD) 2) sympathetic activity 3) parasympathetic activity	*1) CMAI:* significant reduction of agitation in the post-test and post-three week test, stronger in the aroma-acupressure group than in the aromatherapy group compared with control group ($P = 0.01$) *2) sympathetic activity:* significantly lower activity in the 4 week in the aroma-acupressure group and in the 2 week in the aromatherapy group ($P < 0.01$) *3) parasympathetic activity:* significantly higher activity from the 2 week to the 4 week in the aroma-acupressure group and in the 4 week in the aromatherapy group ($P < 0.01$, $p = 0.01$)
Rodriguez -Mansilla et al. (2015)	1) DOLOPLUS2 Scale (pain) 2) CSDD (depression) 3) Campbell Scale (anxiety)	*1-3) DOLOPLUS, CSDD und Campbell Scale:* One-way ANOVA provided consistently significant results ($P < 0.001$) at each stage, and the C showed a deterioration in all cases in relation to the mean compared with other groups
Mariko et al. (2015)	1) NPI (BPSD) 2) MMSE (cognitive deficit) 3) BI (activities of daily living)	*1) NPI*: significant decrease of NPI scores from baseline to the end-point in I (25 ± 14 *vs* 16 ± 13; $P < 0.05$), but not in C *2 und 3) MMSE und BI*: no significance regarding both groups for both scores
Moyle et al. (2014)	1) CMAI (BPSD) 2) Observed Emotion Rating Scale (mood)	*1) CMAI:* greater increase in the quiet presence group than the foot massage group for subscale verbal aggression ($P = 0.03$) no significance for other subscales *2) Observed Emotion Rating Scale:* no significant differences
Satoh et al. (2013)	1) MMSE (cognitive deficit) 2) BI (activities of daily living) 3) Computerized tomography scan of the brain 4) NPI (BPSD)	*1 und 2) MMSE und BI:* no significance regarded in both groups for both scores *4) NPI:* significantly lower NPI score from baseline to post-test in I but not in C ($P < 0.05$)
Fu et al. (2013)	1) MMSE (cognitive deficit) 2) CMAI (BPSD)	*1) CMAI:* no significant reduction of disruptive behaviour *2) MMSE:* N/A
Kudoh et al. (2009)	1) NPI (BPSD) 2) MMSE (cognitive deficit) 3) BI (activities of daily living)	*1) NPI:* significant decrease of NPI scores from baseline to the end-point in I ($P < 0.01$), but not in C *2 und 3) MMSE und BI:* no significance regarding both groups for both scores

BI = Barthel Index; BPSD = Behavioural and Psychological Symptoms of Dementia; C = Control; CMAI = Cohen Mansfield Agitation Inventory; CSDD = Cornell Scale for Depression in Dementia; I = Intervention; MMSE = Mini Mental State Examination; NPI = Neuropsychiatric Inventory.

et al., 2015; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015; Satoh et al., 2013; Yang et al., 2016a). In the remaining studies, risk was unclear because of a lack of information (Fu et al., 2013; Turten Kaymaz and Ozdemir, 2017, Yang et al., 2015).

3.3.3. Incomplete outcome data (attrition bias)

Three studies had low risk because of not having any dropouts (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013; Yang et al., 2016b). Four studies (Fu et al., 2013; Kwan et al., 2017; Moyle et al., 2014; Yang et al., 2015) did an adequate intention-to-treat analysis; Yang et al. (2016b) did not. Turten Kaymaz and Ozdemir (2017) had a high dropout rate of 44% (22 of 50), with the control group having twice as many dropouts as the intervention group. In the remaining studies, risk was unclear because of insufficient information.

3.3.4. Selective reporting (reporting bias)

Only four studies reported a registered protocol (Kwan et al., 2017; Moyle et al., 2014; Rodriguez-Mansilla et al., 2015; Yang et al., 2015) (Fig. 2).

3.4. Results of individual studies

Table S2 summarises the baseline and post-baseline values and changes in the regarded outcomes.

3.5. Synthesis of results

Three studies investigated change of Barthel Index (Kudoh et al., 2009; Mariko et al., 2015; Satoh et al., 2013). In Satoh et al. (2013) and Kudoh et al. (2009), data was missing, so performing a meta-analysis was impossible. Overall, no benefit in Barthel Index scoring was described.

3.5.1. Effects of manual massage on cohen mansfield agitation inventory

Six studies measured behavioural and psychological symptoms of dementia (especially agitation and aggression) using the total score of the Cohen Mansfield Agitation Inventory (Kwan et al., 2017; Moyle et al., 2014; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2015, 2016a, 2016b). Scaling of the Cohen Mansfield Agitation Inventory was different; thus SMD was used. The results demonstrated that the effect of manual massage on the management of behavioural and psychological symptoms of dementia was statistically significant (SMD = −0.56, 95% CI [−0.95, −0.17], P = 0.005). Heterogeneity was large (P = 0.004, I^2 = 71%). Due to high risk of bias, Turten Kaymaz and Ozdemir (2017) was omitted for sensitivity analyses. Heterogeneity remained large (P = 0.005, I^2 = 74%). However, results still demonstrated significance (SMD = −0.48 CI [−0.89, −0.06], P = 0.02). In the synthesis of the two studies with lowest risk of bias (Kwan et al., 2017; Moyle et al., 2014), results remained significant (SMD = −0.34 CI [−0.68, 0.01], P = 0.05). Heterogeneity was slight (P = 0.60, I^2 = 0%) (Fig. 3).

3.5.2. Effects of manual massage on the Neuropsychiatric Inventory

Three studies measured the total score of the overall Neuropsychiatric Inventory (Kudoh et al., 2009; Mariko et al., 2015; Turten Kaymaz and Ozdemir, 2017). All studies used identical scaling of the Neuropsychiatric Inventory; thus MD was used. There was no significant effect (MD = −16.67 CI [−35.39, 2.05], P = 0.08). Heterogeneity was large (P = 0.07, I^2 = 63%) (Fig. 4).

3.5.3. Effects of manual massage on the Cornell Scale of Depression in Dementia

Three studies measured the effect of massage on the total score of the Cornell Scale of Depression in Dementia (Rodriguez-Mansilla et al., 2015; Yang et al., 2016a, 2016b). All studies used

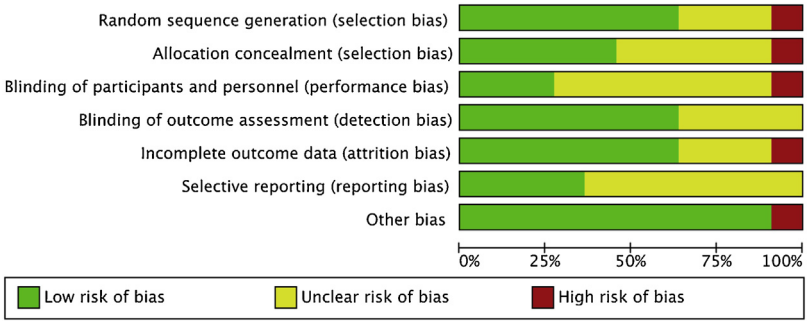

Fig. 2. Risk of bias graph.

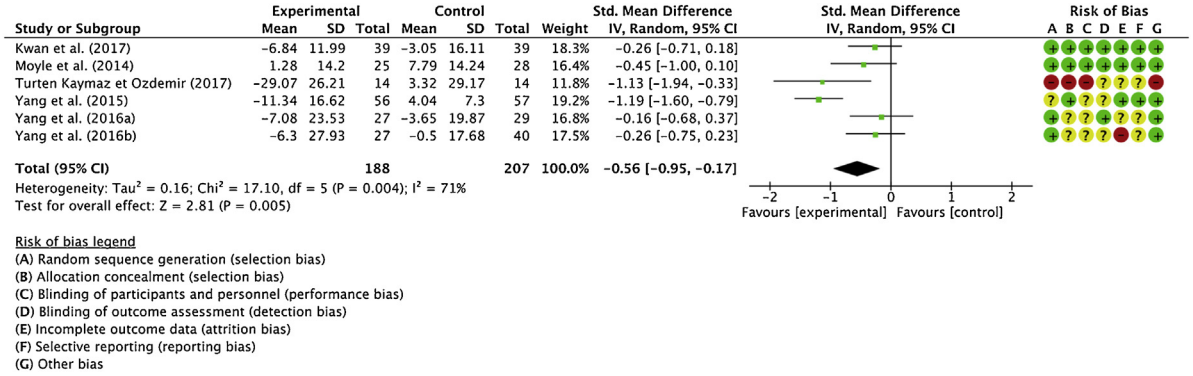

Fig. 3. Effects of manual massage on Cohen Mansfield Agitation Inventory.

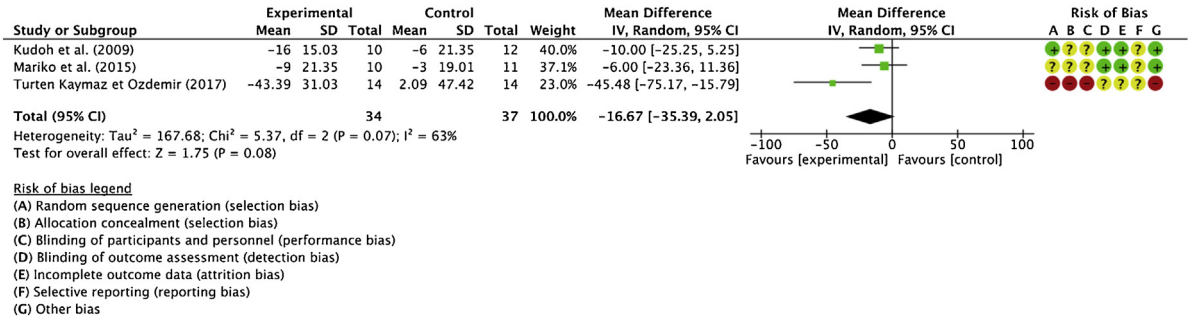

Fig. 4. Effects of manual massage on Neuropsychiatric Inventory.

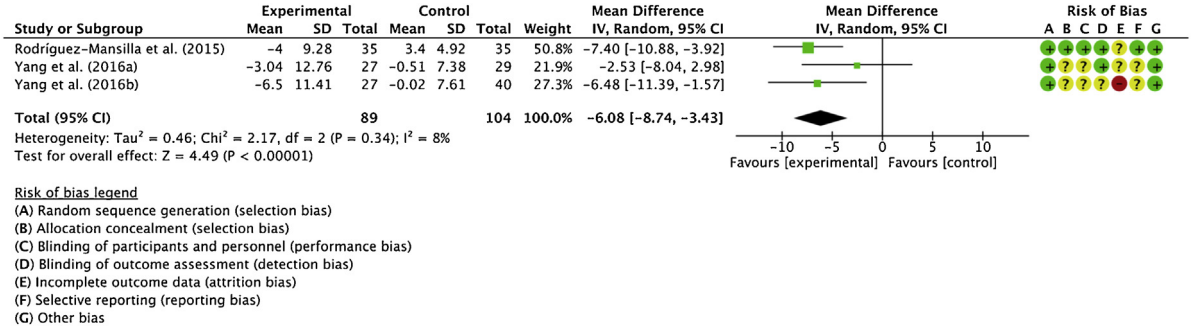

Fig. 5. Effects of manual massage on the Cornell Scale of Depression in Dementia.

identical scaling of the Cornell Scale of Depression in Dementia; thus MD was used. The results demonstrated a significant improvement on the Cornell Scale of Depression in Dementia score (MD = −6.08 CI [−8.74, −3.43], P < 0.00001). Heterogeneity was slight (P = 0.34, I^2 = 8%) (Fig. 5).

3.5.4. Effects of manual massage on the mini mental state examination score

Two studies measured the score of the Mini Mental State Examination (Kudoh et al., 2009; Mariko et al., 2015). Both used identical scaling of Mini Mental State Examination; thus MD was used. The results demonstrated no significant improvement in the Mini Mental State Examination score (MD = 0.00 CI [−5.86, 5.86], P = 1.00). Heterogeneity was slight (P = 1.00, I^2 = 0%). Data were missing in Fu et al. (2013) and Satoh et al. (2013), so they could not be included in meta-analysis of Mini Mental State Examination scoring.

3.6. Risk of bias across studies

Nine studies were included in quantitative syntheses therefore funnel plots were not recommended (Sterne et al., 2011).

3.7. Additional analysis

3.7.1. Subgroup analyses regarding type of manual massage

Four studies compared massage with non-physical contact (Moyle et al., 2014; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2016a, 2016b). SMD was used because of the different scaling of the Cohen Mansfield Agitation Inventory. The results demonstrated significance for massage (SMD = −0.41, 95% CI [−0.75, −0.07], P = 0.02). Heterogeneity was slight (P = 0.23, I^2 = 31%).

Due to the high risk of bias, Turten Kaymaz and Ozdemir (2017) was omitted for sensitivity analyses, and as a consequence results for massage therapy missed the significance level of ≤0.05 (SMD = −0.28 CI [−0.58, 0.02], P = 0.06). Heterogeneity remained slight (P = 0.74, I^2 = 0%).

Two studies compared acupressure with non-physical contact (Kwan et al., 2017; Yang et al., 2015). SMD was used because of the different scaling of the Cohen Mansfield Agitation Inventory. Results demonstrated no significance for acupressure (SMD = −0.73, 95% CI [−1.65, 0.18], P = 0.11). Heterogeneity was large (P = 0.002, I^2 = 89%).

3.7.2. Subgroup analyses regarding outcome measures

A subgroup analysis regarding outcome measure could be performed on the studies using the Neuropsychiatric Inventory (Kudoh et al., 2009; Mariko et al., 2015; Turten Kaymaz and Ozdemir, 2017), the Cornell Scale of Depression in Dementia (Rodriguez-Mansilla et al., 2015; Yang et al., 2016a, 2016b), and the Mini Mental State Examination (Kudoh et al., 2009; Mariko et al., 2015). All studies used identical scaling of their investigated outcome measure, thus MD was chosen. The overall effect showed a significant improvement for manual massage (MD = −5.13, 95% CI [−8.85, −1.40], P = 0.007). Heterogeneity was large (P = 0.07, I^2 = 47%). Sensitivity analysis was indicated and as a consequence Turten Kaymaz and Ozdemir (2017) was omitted. Results remained significant (MD = −5.25, 95% CI [−7.57, −2.94], P < 0.00001). Heterogeneity became slight (P = 0.73, I^2 = 0%).

3.7.3. Subgroup analyses regarding use of oil

Four studies combined their intervention with aromatic oil (Turten Kaymaz and Ozdemir, 2017; Yang et al., 2015, 2016b; Yang et al., 2016a). Three applied the oil during a massage technique not using acupressure (Turten Kaymaz and Ozdemir, 2017; Yang et al., 2016a, 2016b) and one during acupressure of five acupuncture points (Yang et al., 2015). All studies used identical scaling of the Cohen Mansfield Agitation Inventory. Therefore, MD was used. The results demonstrated a significant improvement on CMAI score (MD = −12.32, 95% CI [−21.38, −3.25], P = 0.008). Heterogeneity was large (P = 0.04, I^2 = 64%). Due to high risk of bias, the study of Turten Kaymaz and Ozdemir (2017) was omitted for sensitivity analyses. However, results remained significant (MD = −9.64, 95% CI [−18.00, −1.28], P = 0.02). Heterogeneity remained large (P = 0.08, I^2 = 60%).

Two studies did not combine their intervention with aromatic oil (Kwan et al., 2017; Moyle et al., 2014). They used different scaling of the Cohen Mansfield Agitation Inventory; thus SMD was used. The results were significant (SMD = −0.34, 95% CI [−0.68, 0.01], P = 0.05). Heterogeneity was slight (P = 0.60, I^2 = 0%).

3.7.4. Subgroup analyses regarding treatment duration

Of the Cohen Mansfield Agitation Inventory studies, three had a treatment duration about 200 or more minutes (Kwan et al., 2017; Yang et al., 2015, 2016b) and three studies less than 200 (Moyle et al., 2014; Turten Kaymaz and Ozdemir, 2017; Yang et al., 2016a). Scaling of the Cohen Mansfield Agitation Inventory was different; thus SMD was used. First group passed the significance level (SMD = −0.58, 95% CI [−1.22, 0.06], P = 0.07), whereas second group showed a significant improvement (SMD = −0.50, 95% CI [−1.00, −0.01], P = 0.05). In both groups heterogeneity was large (P = 0.002, I^2 = 84%; P = 0.14, I^2 = 50%). After omitting Turten Kaymaz and Ozdemir (2017) in the second group, significance disappeared (SMD = −0.30, 95% CI [−0.68, 0.08], P = 0.12). Heterogeneity became slight (P = 0.45, I^2 = 0%).

3.8. Other outcome parameters

Secondary outcome parameters in the primary studies were heterogeneous and ranged from caregivers' burden, salivary cortisol, and pain to sympathetic and parasympathetic activity (Table 1). Caregivers' burden was significantly lower in week four after aroma massage (P < 0.05) (Turten Kaymaz and Ozdemir, 2017). Sympathetic activity could be significantly reduced in week four after receiving aroma acupressure, and reverse parasympathetic activity was significantly higher at this time (P < 0.01) (Yang et al., 2015).

4. Discussion

4.1. Results of the meta-analysis

To the best of our knowledge, the current paper is the first meta-analysis examining the mean changes in behavioural and psychological symptoms of dementia outcome measures whilst comparing manual massage with no physical contact in patients with dementia.

The results of the meta-analysis reveal that manual massage improve behavioural and psychological symptoms of dementia and depressive symptoms, demonstrated by significant effects on the Cohen Mansfield Agitation Inventory and the Cornell Scale of Depression in Dementia scores but not on the Neuropsychiatric Inventory. Subgroup analyses regarding the type of intervention demonstrated significant effects for massage with aromatic oil and with interventions not using acupressure. An effect on cognitive deficits measured by the Mini Mental State Examination could not be proven.

4.2. Results of risk of bias assessment

The risk of bias assessment of the included studies is moderate and is mainly caused by the difficulty in blinding within non-pharmacological intervention studies (Boutron et al., 2004). Sensitivity analyses were performed to improve reliability. Altogether, the effect size of our 'observed effects' analyses should be interpreted with caution, however, because of the large confidence intervals estimated for the pooled effect measure. Further high-quality RCTs are needed.

4.3. Literature

Our results are consistent with the meta-analysis of Wu et al. (2017) also demonstrating a significant improvement in behavioural and psychological symptoms. However, Wu et al. (2017) included studies without physical contact and with only one session. This approach is questionable against the background of the oxytocin hypothesis. The current meta-analysis therefore tightened the inclusion and exclusion criteria of intervention situations and considered an intervention period of two to five weeks in order to draw more precise conclusions.

An important aspect is the type of manual massage. The intervention types among our included studies were heterogeneous. The frequent combination with aroma therapy leads to the question as to whether the application of manual massage with aromatic oil has higher effects than manual massage alone. Subgroup analyses in the current study using the Cohen Mansfield Agitation Inventory suggest a greater benefit for manual massage in combination with aromatherapy. In addition to these findings Yang et al. (2015) demonstrated a significant improvement of the Cohen Mansfield Agitation Inventory scores for both interventions together and each of aroma acupressure and aromatherapy alone. The reduction was larger in the aroma acupressure group. This seemingly despite some studies revealing that patients with Alzheimer's disease and Frontotemporal Dementia suffer from olfactory dysfunction (Attems and Jellinger, 2006; Luzzi et al., 2007; McLaughlin and Westervelt, 2008).

We only included studies with manual massage because there is evidence that direct interpersonal contact is processed differently in comparison to similar soft touch but applied through inanimate objects (Kress et al., 2011). Our subgroup analyses of Cohen Mansfield Agitation Inventory scoring showed that massage types not using acupressure were more effective in comparison to acupressure massage. In acupressure the touch is on one spot, while in other types of massage it is more extensive. The results of Schmidt et al. (2000) showed that a tonic pressure stimulation activates mechano-insensitive units more strongly than mechano-responsive units. These differences in the stimulation of unmyelinated C-tactile fibres could lead to a greater release of oxytocin in the posterior pituitary (Walker et al., 2017) during non-acupressure type massage. The release of oxytocin contributes, through widely distributed oxytocin receptors within the central nervous system, to a range of sensory and psychological processes essential for adaptive social behaviour (Mitre et al., 2016; Walker et al., 2017). This leads also to an improvement of cognition and behavioural symptoms in persons living with Frontotemporal Dementia in particular (Jesso et al., 2011; Tampi et al., 2017). Considering these findings, the question arises as to whether nursing activities with skin-to-skin contact such as washing or bathing would also have an impact on behavioural and psychological symptoms in persons living with dementia.

4.4. Limitations

The subgroup findings regarding type of manual massage may be vulnerable to bias due to the different numbers of included studies for massage (non-acupressure type massage n = 4 studies, acupressure type massage n = 2 studies). This is underpinned by the fact that the pooled point estimates derived from the subgroup analyses indicated larger effects of acupressure.

Although we included only studies with validated instruments (Lin and Wang, 2008; Zuidema et al., 2007a, 2007b), so far there is no reliable evidence as to what extent of change among the validated instruments can be regarded as clinically relevant. Zuidema et al. (2011) postulated as clinically relevant a change of 8 using the Cohen Mansfield Agitation Inventory and a change of 11 using the Neuropsychiatric Inventory. The subgroup analysis of the Cohen Mansfield Agitation Inventory reveals a change of about 12 points in our study, which would clearly surpass Zuidema et al.'s (2011) threshold for a clinically relevant change.

However, severity of dementia cannot be measured by a single biological parameter but rather by observing and assessing complex cortical functions like behavioural and psychological symptoms of dementia (Cohen-Mansfield and Billig, 1986). Thus, the difficulty of the assessment of these symptoms complicates the question about clinically relevant change. Further research is needed to help answer this.

4.5. Implications for clinical practice and research

Despite methodological limitations, the benefit of manual massage on behavioural and psychological symptoms in persons living with dementia was demonstrated in our study. Therefore, by massaging patients with dementia, healthcare professionals may help to reduce symptoms and, in turn, reduce the use of sedative medication with dangerous side effects (e.g. neuroleptic drugs). Thus, health care professionals should be encouraged to apply manual massage in persons living with dementia during routine care. Furthermore, as manual massage is easy to apply, it might be a useful strategy to be used by family caregivers in the hope of ameliorating changes in behaviour and mood of the relative living with dementia. It could be used to reduce the caregivers' burden. Therefore, manual massage should be an integral part of family caregiver education programs.

To make clearer recommendations, future studies should include greater sample sizes and provide more information on the type and duration of the applied manual massage.

Contributions of authors

All authors have made substantial contributions to all of the three following criteria:

(1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Differences between protocol and review

Application of models due to statistical heterogeneity check is not recommended (Higgins, 2011); thus a random-effects model was used. To maximize homogeneity, studies with an intervention duration of less than one week were excluded and differences of mean change were considered.

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Conflicts of interest

None.

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Appendix A. Supplementary data

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