Pain and its consequences in dementia: Observing the complex relationship between pain, behaviour and ADL in nursing home residents

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CHAPTER 3

Association between pain, neuropsychiatric symptoms, and physical functioning in dementia: a systematic review and meta-analysis

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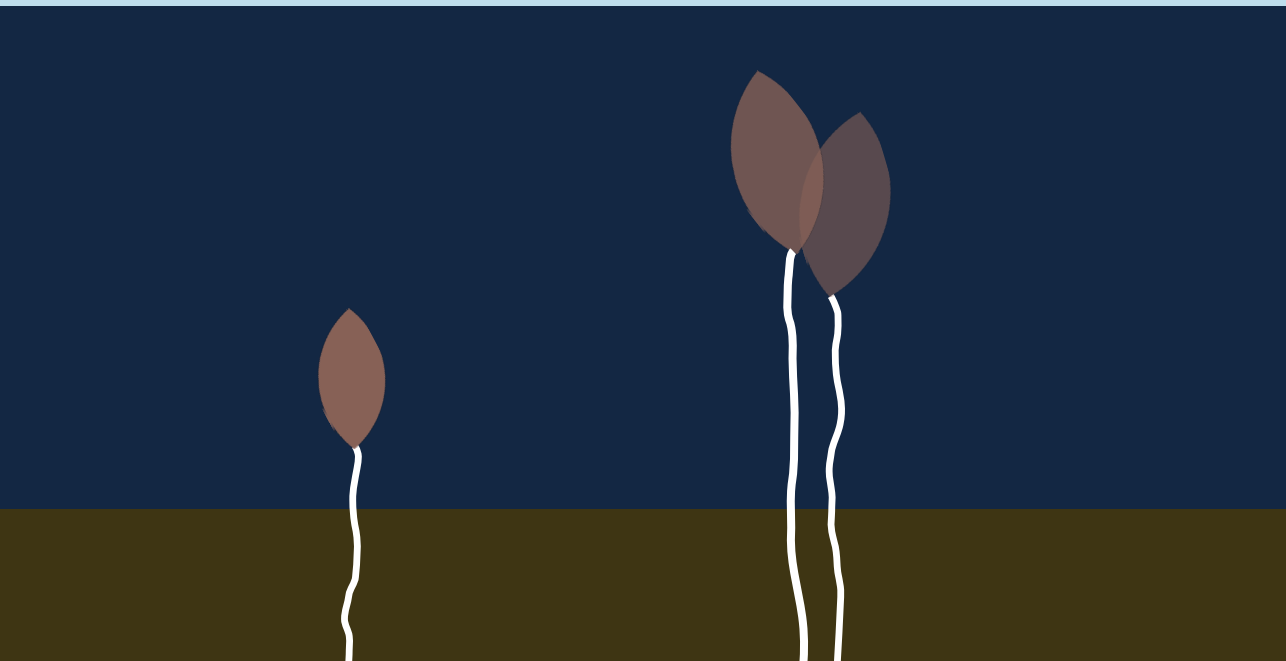
Awarded the 'Jan Stoop Prize' (2015) by the Interfacultair Overleg Specialisme Ouderengeneeskunde. This prize is an incentive price named after Jan Stoop, one of the pioneers of nursing home medicine in the Netherlands (1927-2009)



Abstract

Background

Pain, neuropsychiatric symptoms (NPS) and functional impairment are prevalent in patients with dementia and pain is hypothesized to be causal in both neuropsychiatric symptoms (NPS) and functional impairment. As the exact nature of the associations is unknown, this review examines the strength of associations between pain and NPS, and pain and physical function in patients with dementia. Special attention is paid to the description of measurement instruments and the methods used to detect pain, NPS and physical function.

Methods

A systematic search was made in the databases of PubMed (Medline), Embase, Cochrane, Cinahl, PsychINFO, and Web of Science. Studies were included that described associations between pain and NPS and/or physical function in patients with moderate to severe dementia.

Results

The search yielded 22 articles describing 18 studies, including two longitudinal studies. Most evidence was found for the association between pain and depression, followed by the association between pain and agitation/aggression. The longitudinal studies reported no direct effects between pain and NPS but some indirect effects, e.g., pain through depression. Although some association was established between pain and NPS, and pain and physical function, the strength of associations was relatively weak. Interestingly, only three studies used an observer rating scale for pain-related behaviour.

Conclusion

Available evidence does not support strong associations between pain, NPS and physical function. This might be due to inadequate use or lack of rating scales to detect pain-related behaviour. These results show that the relationship between pain and NPS, as well as with physical function, is complicated and warrants additional longitudinal evaluation.

Keywords:

pain; dementia; neuropsychiatric symptoms; physical function; associations

Background

Pain is common among older persons due to the increased prevalence of age-related diseases like osteoporosis and arthritis.[1] This also applies to patients with dementia living in nursing homes: around 50% is in pain[2 3].
Due to the changed perception of pain and loss of language skills in dementia, pain is often not communicated as such. In these patients, pain is often reported to be expressed as challenging behaviour (e.g., agitation or withdrawal) and is also known as neuropsychiatric symptoms (NPS)[4-6]. NPS includes depressive symptoms, agitated/aggressive behaviour, and psychotic symptoms like hallucinations and delusions[7].
NPS is highly prevalent: up to 80-85% of patients with dementia experience these symptoms[7-9] and they are one of the main reasons for institutionalisation[9 10]. The aetiology of NPS is multifactorial and includes neuropathological changes in the brain related to dementia and dementia severity, as well as unmet physical and psychological needs, physical illness (e.g., urinary tract infections), and pain[11].
Furthermore, pain influences the patient's physical function, including sleep, nutrition, and mobility[12-15]. Therefore, physical inactivity and disability in patients with dementia may be an expression of pain, but can also be the cause of pain[16 17]. This illustrates that, due to its diverse presentation, the interpretation of potential signs and symptoms of pain in dementia is difficult; moreover, to date, most studies still report a systematic under-recognition and under-treatment of pain[18-20]. There is evidence for specific pain-related behaviour, such as increased wandering or irritability, but facial expressions, body movements, and vocalizations are also common[21]. These behaviours can help in the clinical decision-making process[22]. Consequently, in the last decades, measurement and assessment of pain in patients with dementia by means of observations of these behaviours have received increasing attention. However, clinicians still have insufficient tools to face the challenges in the diagnostics and treatment of pain in this vulnerable group[22 23], and this may result in clinical indecisiveness. Nevertheless, there are validated measurement instruments available to detect pain in patients with dementia, such as the PACSLAC, DOLOPLUS-2, and the MOBID-2, based on observations[24 25]. Adequate use of these measurement instruments is of utmost importance in the management of pain.
Due to the challenges in the assessment and management of pain[26], people with dementia and NPS are more likely to receive antipsychotic drugs, despite the adverse side-effects like falls, somnolence and even death[27-29]. The latter underlines the importance of understanding the attributive effect of pain as a cause of NPS and decline in physical function. This would give healthcare workers more insight as to whether to target their treatment primarily on pain, NPS, disability, or on these conditions simultaneously.

Therefore, the aim of this systematic review is to assess the strength of associations between pain and NPS, and between pain and physical function, in patients with dementia. Special attention is paid to the description of measurement instruments and the method of detecting pain, NPS, and physical function to give clinical and scientific direction to the assessment and treatment of pain.

Methods

Study selection

This review was conducted following the PRISMA guidelines for systematic reviews[30]. A systematic search of the following databases was performed in March 2013: PubMed (Medline), Embase, Cochrane, Cinahl, PsychINFO, and Web of Science. In addition, the reference lists of the retrieved articles were screened. The following search terms (Additional file 1) were applied: Dementia AND Pain AND ((depression) OR (BPSD) OR (mobility) OR (sleep) OR (eating) OR (ADL)). Two reviewers, AvD and MP, independently, screened each title and abstract for suitability for inclusion; they decided independently on the eligibility of the article according to the predetermined selection criteria. Disagreement was resolved by consensus after review of the full article, or after the input of a third author (WA/MdW).

Articles that met the following criteria were included: patients with moderate to severe dementia (defined as a Mini Mental State Examination (MMSE) score of ≤ 18 or a Global Deterioration Scale (GDS) score of 5-7[31]), description of data on pain, description of NPS, and/or physical function (eating, sleep, activities of daily living (ADL) and mobility). For the purpose of this review, articles that described patients with mild to moderate dementia, but reported statistical data separately for the subgroup 'moderate dementia', were also included.
Eligible study designs included clinical trials, cohort, cross-sectional, observational, and longitudinal studies. Unless there was a clear description of the original data and baseline statistics, systematic reviews, qualitative studies, study protocols, (editorial) letters, case reports and randomised controlled trials (RCTs) were excluded. However, the reference lists of these articles were screened for eligible studies that were missed during the initial search. Only published data was included.
Excluded were articles that described patients who suffer from dementia resulting from Parkinson's disease and Huntington's disease, AIDS dementia complex, and Creutzfeldt-Jakob Syndrome. Furthermore, we excluded articles that did not report correlation coefficients or odds ratio's (OR), or when the articles did not provide sufficient information to calculate the OR ourselves. No time range or language restrictions were used.

Data extraction

Data were independently extracted by two reviewers (AvD and MP). A data extraction form was designed before extracting data from the included articles.
We recorded data on: study characteristics (design, country, setting, study population), pain and NPS measurement, prevalence of pain, and correlations of pain, NPS, and physical function. Where possible we present unadjusted associations, as these reflect the presence of co-occurrence as perceived by the caregivers. In addition, we calculated the OR ourselves if not reported. These ORs are reported as self-calculated odds ratio (SOR).

Furthermore, we recorded data on the use of rating scales to measure pain, NPS and physical function, as well as the method of detection. For example, if pain was measured with a rating scale for observational behaviours indicating pain and who performed the observation, i.e., a research nurse, a professional or patient's proxy.

Quality assessment

The methodological quality assessment of the included cross-sectional and longitudinal studies was based on previously developed checklists[32 33]. Two reviewers (AvD and MP) independently assessed the quality of each study. Disagreement was resolved by consensus or after input of a third author (MdW/WA). The maximum total score possible for cross-sectional studies was 12 points and for longitudinal studies 14 points. Cross-sectional studies that scored 0-4 points were considered to be of 'low quality', scores of 5-9 to be of 'moderate quality', and scores of ≥ 10 points were considered to be of 'high quality'. For longitudinal studies, scores of 0-5 points were considered to be of 'low quality', scores of 6-11 points to be of 'moderate quality', and scores of ≥ 12 points were considered to be of 'high quality'. See Additional file 3 for a more detailed overview of the awarded points and scores to the articles.

Scoring items

We selected items relevant for the assessment of observational studies, such as a description of a clearly stated objective, use of valid selection criteria, a response rate of ≥ 80%, valid/reproducible measurement of the outcome, adjusting for possible confounders, and the presentation of an association. One point was awarded for each question answered with 'yes' and 0 points for every 'no' or '?'. We added two questions concerning the study objective and population: i) was the selected objective similar to our objective, and ii) was the study population a selected population.
Furthermore, we wanted the quality assessment to reflect the ability to study our research objective. Therefore, we added a few items focusing on the measurement of pain, i.e., the use of specific rating scales, the method of detection, and information about the rater. Awarded points ranged from 0-2.
Additionally, two questions were added to the quality assessment for the longitudinal studies: i) was there major and selective loss to follow-up, and ii) was there a sufficiently long follow-up period. Again, 1 point was awarded for each question answered with 'yes' and 0 points for each 'no' or '?'.

Statistical analysis

To provide a more comprehensive overview of the association between pain, NPS and physical function, the available ORs are displayed in forest plots (using the program Review Manager 5.2) including the pooled ORs using a random effects model.

Results

Selected articles

The literature search yielded 1386 articles; 786 from PubMed (Medline), 304 from Embase, 77 from Cinahl, 57 from PsychINFO, 96 from Cochrane, and 66 from Web of Science. Additionally, 22 articles were retrieved from other sources (mainly through checking the reference lists). After removing duplicates, 1091 unique articles were identified. After carefully screening the titles, abstracts and full text, 22 publications met the inclusion criteria and were included in the present review (Figure 1).

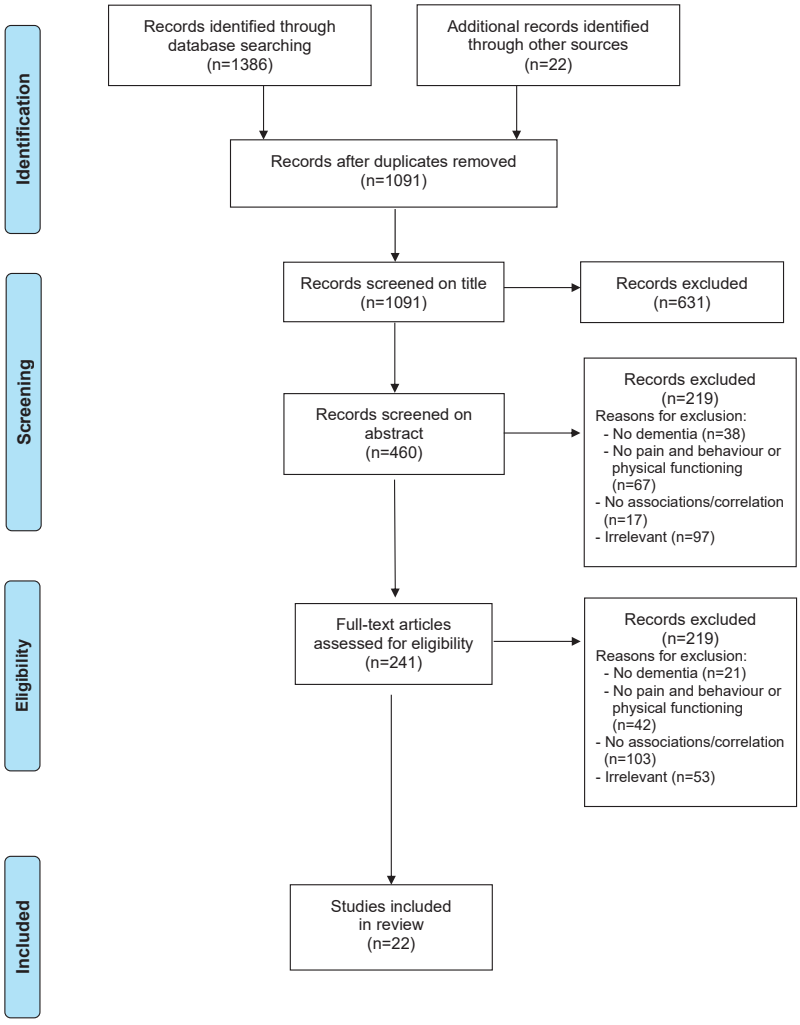


Figure 1. Flow diagram of the inclusion of studies

Description of included studies

All included articles were published between 2002 and 2013.
Of these 22 articles, eight articles illustrate correlates of pain with specified behavioural problems such as delusions/psychosis[3 34], anxiety[35], wandering[3 36], and resistance to care[3 37 38]. Furthermore, seven articles described associations between pain and unspecified behavioural problems, such as behavioural/psychiatric problems and dysfunctional behaviours[3 4 39-43]. It was not clarified which types of NPS were embedded in this term.
Eleven articles described the association between pain and depression[4 8 34 35 43-49] and eight articles between pain and aggression/agitation[8 34 36 38 47 48 50 51].
In addition, relationships between pain and physical function (e.g. ADL dependency and mobility) were described in ten articles[3 4 39 40 43 44 46 48 49 52].
The characteristics of these articles are presented in Table 1.

Table 1. Characteristics of the included studies

First author	*Country, setting*	*Dementia*	*Population: selection on pain, NPS or function?*	*Quality of study***
Ahn 2013 [36]	USA, nh	Moderate dementia, mean MDS cognitive performance scale 3.17 (SD 1.52)	Age ≥65 years, excluded when comatose	10
Bartels 2003 [8]	USA, ltc	Dementia, AD or signs of chronic stable cognitive impairment (in chart or MDS)	At risk for (or having) pressure ulcers	4
Black 2006 [39]	USA, nh	Advanced dementia, SIRS mean 10.3 (SD 6.7), AD 58%	Palliative care (life expectancy ≤6 months)	6.5
Brummel-Smith 2002 [40]	USA, nh	Moderate to severe dementia, MMSE mean 16.8 (SD 5.6) for 92 subjects	Age ≥ 55 years, had to have pain assessment, able to self-report on their level of pain	7
Cipher 2004 [4]	USA, ltc	Moderate dementia, mean NCSE 0.10 (SD 0.91)	Referral to clinical psychologist due to change in cognitive functioning, emotional distress, or behavioural dysfunction associated with dementia	7.5
Cipher 2006 [41]	USA, ltc	Dementia, mild 40%, moderate 41% and severe 19%, according to FAST (Reisberg) NCSE	Referral to clinical psychologist due to change in cognitive functioning, emotional distress, or behavioural dysfunction associated with dementia	7.5
D'Astolfo 2006 [44]	Canada, ltc	In 4% no dementia with MMSE>25, mild dementia 27%, moderate 44%, severe 25%	Admission in ltc at least 6 months to allow for patient charts to be completed	7
Gruber-Baldini 2005 [45]	USA, nh and residential care/ assisted living	Dementia, mild 14%, moderate 26% and severe 61%, according to MMSE or MDS-COGS.	Random sample aged ≥65 years (complete response 60%)	8.5
Kunik 2005 [34]	USA, va outpatients	Dementia, mild 46%, moderate 39%, severe 11%, according to DRS.	Veteran outpatients, not in LTC-facilities, with available caregiver	8.5
Leonard 2006 [50]	USA, nh	Dementia according to CPS-MDS dataset	At least one comprehensive MDS assessment, age ≥ 60 years	9

Table 1. Characteristics of the included studies *(continued)*

First author	*Country, setting*	*Dementia*	*Population: selection on pain, NPS or function?*	*Quality of study***
Leong 2007 [35]	Singapore, nh	Dementia with 33% mild (MIC) and 41% severe (SIC) cognitive impairment, according to AMT	No recent change in cognitive status, age ≥65 years. Here report of *communicative* subgroup *with dementia* (thus excluding 53 and including 125 of 358).	8.5
Lin 2011 [46]	Taiwan, nh	Dementia, 39% profound or end-stage dementia, according to CDR-C. Dementia, DemRS2 mean 4.12 (SD 2.79)	Admission at least 1 month	12
Morgan 2012 [47]	USA, Veterans Administration Medical Centre, longitudinal study		> 60 years, no aggressive behaviour in past year, no residence in nh and caregiver > 8 hrs a week, no onset of aggression before first follow-up (at 5 mo)	9.5
Norton 2010 [42]	USA, nh	Dementia, MMSE mean 6.4 (SD 6.7)	Verbal disruption (BEHAVE-AD >= 1.5), age ≥55 years, passed audiological assessment, and life expectancy >6 mo	9
Shega 2005 [48]	USA, outpatient geriatrics clinic	Dementia, MMSE mean 16.6 (SD 7.2)	Patient-caregiver dyad with pain-report on same day (77% of original sample)	9.5
Shega 2010 [49]	Canada, community dwelling	Cognitive impairment, 3 MS, mild to moderate dementia 18.5%	Community dwelling people aged ≥65 years, within one inclusion wave a pain self-assessment was incorporated	9
Torvik 2010 [52]	Norway, nh	No (13%), mild (46%) or moderate (41%) cognitive impairment, according to MMSE.	MMSE >11, aged ≥65 years (inclusion and response 35% of total sample). Communicative patients	6.5
Tosato 2012 [3]	EU and Israel, nh	Cognitive impairment, mild-moderate 55% and severe 45%, according to CPS	Several countries	11.5
Volicer 2009 [37]	Netherlands, nh/residential home	Dementia, according to MDS-CPS	Dependent in decision making, aged ≥65 years	11
Volicer 2011 [51]	Netherlands, nh, longitudinal study	Dementia, according to MDS	Availability of 4 quarterly MDS assessments within period of 15 months, aged ≥65 years	12
Williams 2005 [43]	USA, nh and residential care/assisted living	Dementia, with 29% MMSE>10 and MDS-COGS >2-4	Available pain data, aged ≥65 years	10
Zieber 2005 [38]	Canada, ltc	Moderate to severe cognitive impairment, according to FAST (Reisberg) score 6-7	Residents with continuous nursing care because of significant physical and/or cognitive impairments ('nh-level')	8

Abbreviations: nh, nursing home; MDS, Minimum Dataset; ltc, long term care facility; AD, Alzheimer's Disease; SIRS, The Severe Impairment Rating Scale; MMSE, Mini Mental State Examination; NCSE, Neurobehavioural Cognitive Status Examination; FAST, Functional Assessment Staging; MDS-COGS, Minimum Dataset Cognition Scale; va, veterans affairs; DRS, Dementia Rating Scale; CPS, Cognitive Performance Scale; AMT, Abbreviated Mental Test; CDR-C, Clinical Dementia Rating Scale-Chinese Version; Dem-RS2, Dementia Rating Scale 2; SD, Standard Deviation; BEHAVE-AD, Behavioural Pathology in Alzheimer's disease** Based on checklists from van der Windt et al.[52,53] Higher scores indicate higher quality (range observational studies 0-12, range longitudinal studie

Most of the studies described patients aged ≥ 65 years, who were mainly diagnosed with moderate to severe dementia and resided in long-term care facilities throughout the USA[4 8 34 36 39-43 45 47 48 50]. Three studies took place in Europe[3 51-53], three studies in Canada[38 44 49], and two studies took place in Asia[35 46].

Of the 20 cross-sectional studies, five studies were considered to be of high quality[3 36 37 43 46]. The remaining 15 studies were of low to moderate quality. Of the two longitudinal studies, that of Volicer et al. was considered to be of high quality[51] (Table 1).

Five studies described the use of selection criteria, mostly on NPS, and in eight other studies there might have been an indirect (unintentional) selection on pain, NPS or functioning. For instance, an indirect selection on pain by including patients with pressure ulcers[8].

Eight articles described the same study populations, sometimes with additional selection criteria, e.g. the two articles by Cipher et al[4 41]. Kunik et al. and Morgan et al. used data from a large longitudinal study on the causes and consequences of aggression in persons with dementia. Another two articles extracted data from the Dementia Care project of the Collaborative Studies of Long-Term Care[43 45] and two articles derived their data from the same Minimum Dataset 2.0 for nursing home care[37 51].

Overview of measurement instruments

Table 2 describes how pain, NPS, and physical function were measured.

Measurement of Pain

Three articles describe rating scales for observational behaviours indicating pain; both scales are validated for patients with moderate to severe dementia, i.e., the PAINAD[35 46] and DS-DAT[38]. The remaining articles describe other methods to measure pain (Additional file 2); some articles used the MDS dataset[3 36 37 50 51] and others used a variety of rating scales, e.g., the Faces Pain Scale[40], the Geriatric Multidimensional Pain and Illness Inventory[4 41], the Proxy Pain Questionnaire[52] and the Philadelphia Geriatric Center Pain Intensity Scale[34 43 45 47]. The Verbal Descriptive Scale and Verbal Rating Scale were also used to measure pain, sometimes combined with self-report[48 49 52]. Three articles used no rating scales to measure pain; they extracted data form patient's medical records[8 44] and interviewed patient's proxy and/or healthcare worker[39].

Additional file 2 provides a complete overview of the methods used.

Table 2. Measurements of pain, neuropsychiatric symptoms and physical function

	Measurement of pain		*Measurement of neuropsychiatric symptoms*		*Measurement of function*	
First author	***Rating scale***	***Method of detection***	***Rating scale***	***Method of detection***	***Rating scale***	***Method of detection***
Ahn 2013 [36]	MDS pain severity scale, combining pain frequency and pain intensity	Self-report, if not possible staff report based on proxy reports	MDS subscales; wandering-item, aggression behaviour scale (ABS), challenging behaviour profile (CBP) agitation subscale	Patient self-report, proxy and professional	MDS-ADL long form (7 items)	Staff observation
Bartels 2003 [8]	No use of rating scale	Data collection instrument (3-month period), raters unknown	MDS for depression	Medical records	MDS (number of ADLs)	Medical records
Black 2006 [39]	No use of rating scale	Medical records, preceding 6 months, interview surrogate and physician	No use of rating scales	Medical records, preceding 6 months, interview proxy and staff	No use of rating scale	Medical records, preceding 6 months, interview proxy and staff
Brummel-Smith 2002 [40]	1 out of 3 scales: faces or line scale, or word-based pain intensity scale	Self-report, assessed by trained research assistants	No use of rating scales	Trained research assistants	No use of rating scale	Trained research assistants
Cipher 2004 [4]	GMPI pain and suffering subscale	Part of neuropsychological evaluation by a licensed clinical geropsychologist	-GDS-15 -26 dysfunctional behaviours with scores 1-7	Part of neuropsychological evaluation by a licensed clinical geropsychologist	PRADLI	Part of neuropsychological evaluation by a licensed clinical geropsychologist
Cipher 2006[41]	GMPI	Part of neuropsychological evaluation by a licensed clinical geropsychologist and each instrument was administered after interviewing the resident, nursing staff and family members	GLDS, 19 categories with scores 1-7	Part of neuropsychological evaluation by a licensed clinical geropsychologist and each instrument was administered after interviewing the resident, nursing staff and family members Medical records, preceding 6 to max 26 months	GLDS	Part of neuropsychological evaluation by a licensed clinical geropsychologist and each instrument was administered after interviewing the resident, nursing staff and family members

D'Astolfo 2006[44]	No use of rating scale	Medical records, preceding 6 to max 26 months	No use of rating scales		No use of rating scale	Medical records Ambulatory status: independent, requires assistance, wheel chair (or bedridden n=1)
Gruber-Baldini 2005[45]	PGC-PIS, score ≥2	Rating by supervisory staff member	CSDD CMAI	Rating by supervisory staff member	MDS; activities of daily living scale, SMOI	Rating/observation by supervisory staff member
Kunik 2005[30]	PGC-PIS, item on level of pain in previous week, scores 1-6	Interview with patient and proxy by trained interviewer/research assistant	CMAI HAM-D NPI (subdomains delusion/ hallucinations)	Interview with patient and proxy by trained interviewer/research assistant	-	-
Leonard 2006[50]	MDS pain burden using a 4-level composite score based on pain frequency and intensity	-	MDS (Physical aggression: MDS item 'others were hit, shoved, scratched, sexually abused'; Depression: MDS score ≥3 on sum of 9 items, e.g. 'being sad', 'making negative statements', 'persistent anger with self or others', 'pained facial expressions'. (At least once in week before)	-	-	-
Leong 2007[35]	PAINAD for non-communicative patients	Interviews with patient and staff member by professionals for communicative patients	Depression with GDS-15 or STAI Anxiety with Cornell	Self-report or staff report	AAS	Not reported
Lin 2011[46]	PAINAD-Chinese version	Observation immediately following instances of routine care by principal investigator and research assistant	No use of rating scales	Medical records and observations by professional	No use of rating scale	Medical records and observation by professional

Table 2. Measurements of pain, neuropsychiatric symptoms and physical function *(continued)*

	Measurement of pain		*Measurement of neuropsychiatric symptoms*		*Measurement of function*	
First author	***Rating scale***	***Method of detection***	***Rating scale***	***Method of detection***	***Rating scale***	***Method of detection***
Morgan 2012[47]	PGC-PIS worst pain item	Not reported	CMAI aggression subscale CMAI non-aggressive physical agitation subscale HAM-D depression	Not reported	-	-
Norton 2010[42]	PPQ, intensity item, 10-14 day baseline	Primary CNA and data used from medical records	RMBPC-NH, selection of 3 need driven behaviours, BEHAVE-AD	Primary CNA and unit staff	PSMS	Nurses and trained research assistants
Shega 2005[48]	VDS, 1 item on presence and severity of pain 'right now'	Interviews with patients and caregivers by trained research assistant	GDS-15 CMAI	Interview patient and proxy	KATZ IADL	Interview patient and proxy
Shega 2010[49]	VDS, 5-point, 'pain past 4 weeks'	Interviews with patient by trained research assistant	Mental Health screening questionnaire; 5-item and 6-point scale	Interview with patient by trained research assistant	OARS/IADL; 3-point scale	Interview patient by trained research assistant
Torvik 2010[48]	VRS, 4-point, 'pain right now'	Patient self-report	DQoL, 29-items on 5 domains: self-esteem, aesthetics, positive affect, negative affect, belonging	Not reported	Barthel	Self-report and medical records
Tosato 2012[3]	InterRAI LTCF	InterRAI LTCF questions and observation of behaviour, any type of pain or discomfort of the body in previous 3 days by trained (research) staff	InterRAI LTCF 5 behavioural symptoms, previous 3 days	Not reported	MDS ADL Hierarchy Scale	Data recorded by study physicians

Volicer 2009 [37]	MDS-RAI pain frequency (item J2a)	Combination of physical examination, patient history, observation, consultation caregiver and medical records by staff	MDS Depression Rating Scale MDS item J1e for delusions MDS item J1i for hallucinations	Combination of physical examination, patient history, observation, consultation caregiver and medical records by staff	-	-
Volicer 2011 [51]	MDS	Combination of physical examination, patient history, observation, consultation caregiver and medical records by staff	MDS items I1ee, E1a, E1d, E1f, E1b, E1i, E1l, E1m for depression MDS for delusions and hallucinations MDS items B5b, E1b, E4aa, E4da for agitation	Combination of physical examination, patient history, observation, consultation caregiver and medical records by staff	-	-
Williams 2005 [43]	PGC-PIS, score ≥2, and 0-10 pain numeric rating scale	Registered nurses or licensed practical nurses and interview with overseeing supervisor	CSDD, score ≥7 CMAI, any behaviour at least weekly	Rating by care supervisors, registered nurses and licensed practical nurses	MDS-ADL, APAS SMOI	Rating by care supervisors, registered nurses and licensed practical nurses
Zieber 2005 [38]	DS-DAT, and a 7-point pain rating scale	Trained facility nurses, palliative care nurse consultants	PAS	Trained facility nurses	-	-

Abbreviation: MDS, Minimum Dataset; ADL, Activities of Daily Living; GMPI, Geriatric Multidimensional Pain and Illness Inventory; GDS-15, Geriatric Depression Scale-15 short version; PRADLI, Psychosocial Resistance to Activities of Daily Living Index; GLDS, Geriatric Level of Dysfunction Scale; PGC-PIS, Philadelphia Geriatric Centre Pain Intensity Scale; CSDD, Cornell Scale for Depression in Dementia; CMAI, Cohen-Mansfield Agitation Inventory; SMOI, Structured Meal Observational Instrument; HAM-D, Hamilton Rating Scale for Depression; NPI, Neuropsychiatric Inventory; PAINAD, Pain Assessment in Advanced Dementia; STAI, State-Trait Anxiety Inventory; AAS, Adjusted Activity Scale; PPQ, Proxy Pain Questionnaire; CNA, Certified Nursing Assistant; RMBPC-NH, Revised Memory and Behaviour Problems Checklist-Nursing Home; BEHAVE-AD, Behavioural Pathology in Alzheimer's disease; PSMS, Physical Self Maintenance Scale; VDS, Verbal Descriptor Scale; KATZ, Index of Independence in Activities of Daily Living; IADL, Instrumental Activities of Daily Living; OARS/IADL, Older Americans Recourses and Services/Instrumental Activities of Daily Living; VRS, Verbal Rating Scale; DQol, Dementia Quality of life; APAS, Albert Patient activity Scale; DS-DAT, Discomfort Scale - Dementia of Alzheimer Type; PAS, Pittsburgh Agitation Scale

Measurement of NPS

There was no uniform way of reporting NPS. The terms 'behavioural symptoms', 'psychiatric symptoms', and 'disruptive behaviour' were commonly used to describe any type of behavioural symptoms, e.g., agitation, depression, and anxiety[3 4 39-41].
The most common type of reported NPS was depression, followed by symptoms such as wandering, resistance to care, and verbal or physical abuse[36 37 42]. Four articles used no rating scales to measure NPS; they screened medical records instead[8 39 44 46]. Nine articles used more than one rating scale simultaneously to asses NPS[4 34 35 42 43 45 47 49 50]. Eight of those articles used rating scales to assess behaviour in patients with dementia; the Cornell Scale for Depression in Dementia[43 45], the Cohen-Mansfield Agitation Inventory[34 43 45 47 49], Behavioural Pathology in Alzheimer's disease[42], and the Neuropsychiatric Inventory[34] (Table 2). One article used the Mental Health screening questionnaire to assess depressed mood[49]. The MDS Dataset was also frequently used[8 36 37 50 51].

Measurement of Physical Function

Physical function was described in eleven articles[3 4 39 40 43-46 48 49 52]. Types of physical function that were reported in the articles are malnourishment[39 43 45], ADL dependency[3 4 40 43 49 52], and mobility[43 44 46].
Five articles used the MDS-ADL scale for measuring patient's physical function (Table 2). This was also the most frequently used measurement[3 8 36 43-45].

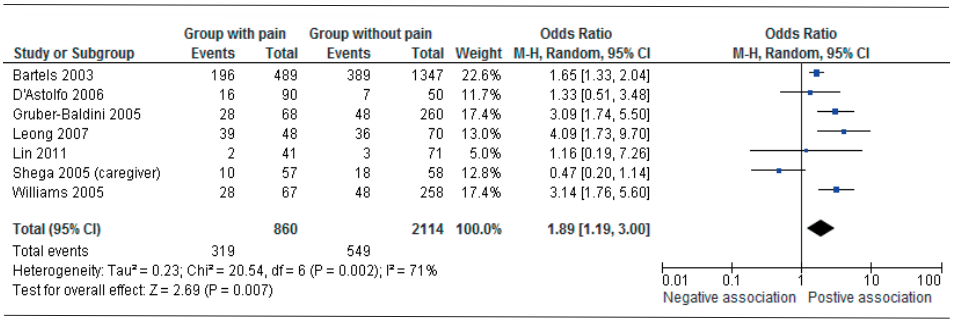
Associations between pain, NPS and physical function

Tables 3, 4, 5 and 6 describe the associations between pain, NPS, and physical function.
In total we found 81 associations expressed in either ORs or correlations. The prevalence rates of pain, NPS, and impairment of physical function ranged from 19-72%[3 4], 2-85%[37 39] and 12-92%, respectively[40 43 45]. Of the 22 included articles, the ORs could be extracted in six and the correlation coefficient in nine articles; in addition, we could calculate the SOR for the associations in ten articles.

Pain and neuropsychiatric symptoms

The most commonly described associations were between pain and depression (Table 3), pain and agitation (Table 4), and pain and specified NPS (Table 5), such as a negative association between pain and wandering, resistance to care, physical and verbal abuse, and aberrant vocalizations[3 36-38].
Eleven articles described associations between pain and depression (Table 3); in seven of these there was a positive association, with three articles reporting a strong association with an OR > 3 or r=0.5. In four articles the association was not significant: one article did not use a rating scale but examined medical records, one article used the rating scale PAINAD to measure pain, one article measured pain by observations, and another article used self-report. Remarkably, in the study by Shega et al. the OR for pain and depression was lower when pain was rated by the caregiver compared to the self-report of pain:

OR 0.47 (95% CI: 0.20-1.14) and OR 1.52 (95% CI: 0.63-3.68), respectively[48]. We could include seven articles in the meta-analysis (see Figure 2) and the pooled OR for pain and depression was 1.84 (95% CI 1.23-2.80).



Note: Studies with a large sample size (e.g., studies using the MDS dataset) were awarded more weight in the meta-analysis. However, this is not necessarily correct because, in observational studies, a larger sample size does not necessarily mean that these studies are of good methodological quality.

Figure 2. Forest plot: Pain and Depression

Eight articles described cross-sectional associations between pain and agitation/aggression (Table 4): four found positive associations, one found a negative association, two found no association, and one study found no association with pain self-report but a positive association with caregiver pain report. The strongest correlation found was in the study by Zieber et al., i.e., r=0.51 ($p<0.01$) between the DS-DAT scores and agitation.
Interestingly, two articles reported on longitudinal changes with follow-up data. In veterans living at home without aggressive behaviour in the preceding year or in the first five months of follow-up, Morgan et al. found that depression indirectly predicted the onset of aggression through pain[47]. In an unselected population Volicer et al. found that changes in agitation scores were related to changes in depression score but not to pain[51].

Table 3. Correlates of Pain with Depression

First author	*N*	*Pain: prevalence*	*Depression: prevalence*	*Correlates of pain with depression*	*Quality of study*
Bartels 2003 [8]	1836	Pain 27%	Depression 32%	**SOR 1.6 (95% CI: 1.3-2.0)**	4
Cipher 2004 [4]	234	Persistent pain 72%	Depression (GDS-15) mean 7.8 (SD 3.12)	Correlations with GMPI 'pain and suffering' **r=0.13 (p<0.05)** with GDS-15 depression	7.5
D'Astolfo 2006[44]	140	Pain 64% (musculoskeletal pain 40%)	Depression 16%	SOR 1.3 (95% CI: 0.5-3.5) (analyses in sample of no dementia-severe dementia)	7
Gruber-Baldini 2005 [45]	328	High pain 21%	Depression 23%	**SOR 3.1 (95% CI: 1.7-5.5)** (n=328)	8.5
Kunik 2005 [34]	99	Pain mean (PGC-PIS) 2.4 (SD 1.2)	Depression (HAM-D) mean 7.7 (SD 6.1)	**r=0.49 (p ≤ 0.01)**	8.5
Leong 2007 [35]	225	Pain 44%; chronic pain 34%	Depression 61%	**SOR 3.2 (95% CI: 1.8-5.9)**	8.5
Lin 2011 [46]	112	Observed pain 37% (PAINAD >= 2)	Depression 5%	OR=1.2 (95% CI: 0.19-7.26)	12
Morgan 2012 [47]	171	Worst pain mean 1.91 (SD 1.53)	Depression (HAM-D) mean 6.16 (SD 5.28)	Baseline: r = 0.30 (n.s.)	9.5
Shega 2005 [48]	115	Any current pain self-report 32%, caregiver report 53%	Depression (GDS-15) mean 3.1 (SD 2.7)	*For self-report pain* SOR 1.5 (95% CI: 0.6-3.7) *For caregiver pain report:* SOR 0.5 (95% CI: 0.2-1.1) with patient depression	9.5
Shega 2010 [49]	5549	Moderate or greater pain: 35.8%	Depressed mood 37.3%	**OR=1.69 (95% CI: 1.18-2.44)** with depressed mood (Adjusted for demographics)	9
Williams 2005[43]	331	Pain 21%, in nh 23%, in rc/al 20% *(self-report for subgroup mmse>10 was: 39% and 25%)*	Depressed 23%	**OR=2.3 (1.1-4.8)** and **AOR=2.9 (1.2-7.2)** (Adjusted for: sex, race, age, cognitive status, number of 10 comorbidities, impairments of 7 activities of daily living)	10

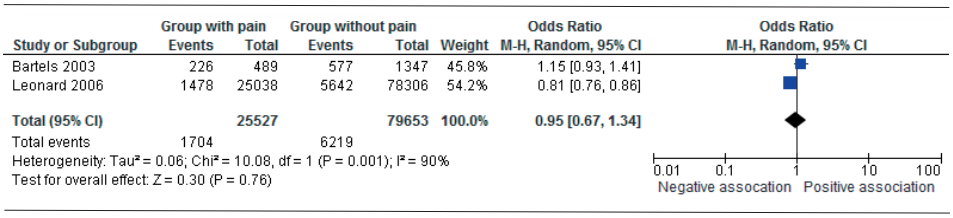
Abbreviations: SOR, Self-Calculated Odds Ratio; SD, Standard Deviation; r, correlation coefficient; AOR, Adjusted Odds Ratio; OR, Odds Ratio; n.s., not significant; GMPI, Geriatric Multidimensional Pain and Illness Inventory; PGC-PIS, Philadelphia Geriatric Centre Pain Intensity Scale

Table 4. Correlates of Pain with Agitation/aggression

First author	*N*	*Pain: prevalence*	*Agitation/ aggression: prevalence*	*Correlates of pain with agitation/aggression*	*Quality of study*
Ahn 2013 [36]	56577	Not reported	Aggression 24% Agitation 24%	**AOR 1.04 (95% CI: 1.01-1.08)** with aggression **AOR 1.17 (95% CI: 1.13-1.20)** with agitation *Subsample without use of psychotropic medication* **AOR 1.07 (95% CI: 1.01-1.15)** with aggression **AOR 1.16 (95% CI: 1.08-1.25)** with agitation (Adjusted for cognition, ADL, sociodemographics)	10
Bartels 2003 [8]	1836	Pain 27%	Agitation 44%,	SOR 1.1 (95% CI: 0.9-1.4) with agitation	4
Kunik 2005 [34]	99	Pain mean 2.4 (SD 1.2)	Agitation (CMAI) mean 14.3 (SD 4.1)	**r=0.20 (p≤0.05)** with aggression	8.5
Leonard 2006[50]	103344	Pain 24%; mild pain 15%, moderate to severe pain 9%	Physical aggression 7%	**SOR 0.8 (95% CI: 0.8-0.9)** for pain burden and physical aggression	9
Morgan 2012[47]	171	Worst pain mean 1.91 (SD 1.53)	Non agressive physical agitation (CMAI) mean 12.14 (SD 4.50)	Baseline: r = 0.06 (n.s.) with aggression *Follow-up:* depression indirectly predicted onset of aggression, through pain	9.5
Shega 2005 [48]	115	Any current pain self-report 32%, caregiver report 53%	Agitation (CMAI) mean 46.9 (SD 18.9),	*For self-report pain* no association with agitation (p>0.05) *For caregiver pain report* p=0.04 with agitation	9.5
Volicer 2011 [51]	1101	Any pain 49%	Agitation (score>0, range 0-5) 76%	**r=0.22 to 0.26 (p<0.001)** with agitation (Range of correlations scores over 4 periods.) *Follow-up:* Longitudinal changes in agitation scores are related to changes in depression score but not to pain.	12
Zieber 2005 [38]	58	Not reported	Not reported	**r=0.51 (p<0.01)** for DS-DAT scores and agitation (PAS-total) <u>Pain rating by palliative care nurse consultants:</u> **r=0.49 (p<0.01)** with agitation (PAS-total) <u>Pain rating by facility nurse:</u> **r=0.28 (p<0.05)** with agitation (PAS-total)	8

Abbreviations: AOR, Adjusted Odds Ratio; ADL, Activities of Daily Living; SOR, Self-Calculated Odds Ratio; SD, Standard Deviation; r, correlation coefficient; n.s, not significant; CMAI, Cohen Mansfield Agitation Inventory; DS-DAT, Discomfort Scale- Dementia of Alzheimer Type; PAS, Pittsburgh Agitation Scale

Furthermore, in a subsample of patients with moderate dementia without the use of psychotropic medication, the association between pain and agitation/aggression was similar compared to residents who used psychotropic drugs[36]. Only two articles could be incorporated in the meta-analysis (see Figure 3) resulting in a pooled OR of 0.95 (95% CI 0.67-1.34).



Note: Studies with a large sample size (e.g., studies using the MDS dataset) were awarded more weight in the meta-analysis. However, this is not necessarily correct because, in observational studies, a larger sample size does not necessarily mean that these studies are of good methodological quality.

Figure 3. Forest plot: Pain and Agitation/Aggression

Table 5 describes NPS, other than depression and agitation/aggression. Relations between pain and anxiety, hallucinations and delusions, were rarely studied. Only one article described an association between pain and anxiety, which was positive: SOR 1.8 (95% CI 1.0-3.0)[35]. Two articles described psychosis and delusions as being related to pain[3 34]. Kunik et al. found a small but non-significant association (r=0.15; p>0.05) with psychosis and Tosato et al. found an OR of 1.5 (95% CI 1.07-2.03) between pain and delusions.
Furthermore, terms like 'behavioural/psychiatric problems' and 'disruptive behaviour' were also frequently used to describe unspecified NPS (Table 5). Two out of seven articles reported moderate positive associations, with r=0.22 (p<0.05) as the strongest correlation between pain and dysfunctional behaviour[4].

Table 5. Correlates of Pain and Neuropsychiatric symptoms

Correlates of pain and specified NPS					
First author	***N***	***Pain: prevalence***	***Neuropsychiatric symptoms: prevalence***	***Correlates of pain with NPS***	***Quality of study***
Ahn 2013 [36]	56577	Not reported	Wandering 9%	**AOR 0.77 (95% CI: 0.73-0.81)** with wandering Subsample without psychotropic medication: **AOR 0.72 (95% CI: 0.63-0.83)** with wandering (Adjusted for cognition, ADL, sociodemographics)	10
Kunik 2005 [34]	99	Pain mean 2.4 (SD 1.2)	Delusions/ hallucinations mean 0.35 (SD 0.48)	**r=0.15 (p>0.05)** with psychosis	8.5

Table 5. Correlates of Pain and Neuropsychiatric symptoms *(continued)*

Correlates of pain and specified NPS					
First author	***N***	***Pain: prevalence***	***Neuropsychiatric symptoms: prevalence***	***Correlates of pain with NPS***	***Quality of study***
Leong 2007 [35]	225	Pain 44%, chronic pain 34%	Anxiety 48%	**SOR 1.8 (95% CI: 1.0-3.0)** with anxiety	8.5
Norton 2010 [42]	161	Not reported	BEHAVE-AD mean 6.4 (SD 29.2) RMBPC-NH mean 1.45 (SD 0.64)	r=0.15 (p=0.08) for pain intensity and emotional behaviour problems r=0.05 (p=0.58) for pain intensity and resistiveness to care	9
Torvik 2010 [52]	106	Current pain in total group 55%, in cognitive impaired group 52%	Negative affect index (DQoL) mean 2.0 (SD 0.75), positive affect/humour index (DQoL) mean 3.4 (SD 0.9)	**p<0.01** for current pain and negative affect p=0.11 for current pain and with positive affect/humour	6.5
Tosato 2012 [3]	2822	Any pain 19% (moderate/ severe/ excruciating pain 13%)	Behavioural symptoms 37% Psychiatric symptoms 21%	**AOR=0.74 (95% CI: 0.55-1.0)** with wandering **AOR=1.4 (95% CI: 1.08-1.8)** with resistance to care **AOR 1.5 (95% CI: 1.07-2.03)** with delusions AOR 1.06 (95% CI: 0.80-1.41) with verbal abuse AOR 1.08 (95% CI: 0.75-1.55) with physical abuse (Adjusted for age, gender, country, cognitive impairment, number of diseases, ischemic heart disease, stroke, falls, communication problems, and a flare-up of a chronic or recurrent condition)	11.5
Volicer 2009 [37]	929	Daily pain 29%, less than daily pain 19%	Verbally abusive not easily altered 2%, physically abusive not easily altered 12% Delusions 8% Hallucinations 9%	r=0.07 (p=0.03) for pain frequency and verbal abuse AOR=0.9(p=0.53) with resisting care AOR=0.7 (p=1.2) with verbal abuse AOR=0.7 (p=0.16) with physical abuse (Both multivariate models among others controlled for resisting care)	11
Zieber 2005 [38]	58	Not reported	Not reported	**r=0.46 (p<0.01)** for DS-DAT scores and resisting care **r=0.42 (p<0.01)** for DS-DAT scores and aberrant vocalization *Pain rating by palliative care nurse consultants:* **r=0.51 (p<0.01)** with resisting care **r=0.40 (p<0.01)** with aberrant vocalizations *Pain rating by facility nurse:* **r=0.48 (p<0.01)** with resisting care **r=0.065 (p<0.63)** with aberrant vocalizations	8

Table 5. Correlates of Pain and Neuropsychiatric symptoms *(continued)*

Correlates of pain and specified NPS					
First author	***N***	***Pain: prevalence***	***Neuropsychiatric symptoms: prevalence***	***Correlates of pain with NPS***	***Quality of study***
Black 2006 [39]	123	Pain 63%	Psychiatric disorders or behaviour problems 85%, behaviour problems 67%	SOR 1.9 (95% CI: 0.7-5.3) with psychiatric/ behaviour problems SOR 1.2 (95% CI: 0.5-2.5) with behaviour problems	6.5
Brummel-Smith 2002 [40]	104 (excluding those unable to self-report pain)	Moderate-severe pain 60% No-mild pain 40% 50 subject unable to answer	≥1 disruptive behaviours (wandering, verbal disruption, physical aggression, regressive behaviour, hallucinations) 70% in dementia sample n=154	SOR 1.8 (95% CI: 0.8-4.0) with ≥1 disruptive behaviour	7
Cipher 2004 [4]	234	Persistent pain 72%	Dysfunctional behaviours mean 4.4 (SD 0.76)	**r=0.22 (p<0.05)** with dysfunctional behaviours	7.5
Cipher 2006 [41]	277	Acute pain 29% Chronic pain 59%	-	**r=0.18 (p<0.05)** with GLDS mean behavioural intensity	7.5
Norton 2010 [42]	161	Not reported	BEHAVE-AD mean 61.4 (SD 29.2) RMBPC-NH mean 1.45 (SD 0.64)	r=0.18 (p=0.03) for pain intensity and disruptive behaviour problems r=0.05 (p=0.53) for pain intensity and global need driven behaviours	9
Tosato 2012 [3]	2822	Any pain 19% (moderate/ severe/ excruciating pain 13%)	Behavioural symptoms 37% Psychiatric symptoms 21%	**AOR=1.4 (95% CI: 1.04-1.8)** with socially inappropriate behaviour (Adjusted for age, gender, country, cognitive impairment, number of diseases, ischemic heart disease, stroke, falls, communication problems, and a flare-up of a chronic or recurrent condition)	11.5
Williams 2005 39	331	Pain 21%, in nh 23%, in rc/al 20% (self-report for subgroup mmse>10 was higher: 39% and 25%)	Behavioural symptoms 58%	OR=1.1 (95% CI: 0.49-2.29) and AOR=1.2 (95% CI: 0.57-2.36) with behavioural symptoms (Adjusted for: sex, race, age, cognitive status, number of 10 comorbidities, impairments of 7 activities of daily living)	10

Abbreviations: AOR, Adjusted Odds Ratio; ADL, Activities of Daily Living; SD, Standard Deviation; r, correlation coefficient; SOR, Self-Calculated Odds Ratio; BEHAVE-AD, Behavioural Pathology in Alzheimer's disease RMBPC-NH, Revised Memory and Behaviour Problems Checklist-Nursing Home; DQoL, Dementia Quality of life; DS-DAT, Discomfort Scale- Dementia of Alzheimer Type; GLDS, Geriatric Level of Dysfunction Scale; rc/al, residential care/assisted living; MMSE, Mini Mental State Examination; OR, Odds Ratio

Pain and physical function

Eleven articles reported associations between pain and physical function, although in most cases this was not the main topic of the study (Table 6). We found associations between pain and ADL or iADL impairment[3 4 40 48 49 52]. One article reported a positive association between pain and iADL impairment: OR 1.74 (95% CI 1.15-2.62). Other associations (although not significant) with physical impairment described in the articles were immobility[44 46] and malnourishment[43].

Only two articles described a positive association: one study used the PAINAD to objectify pain and one study used a five-point verbal descriptive scale to measure pain and a three-point scale (OARS/IADL) to measure functional impairment[46 49].

Table 6. Correlates of Pain with Physical Function

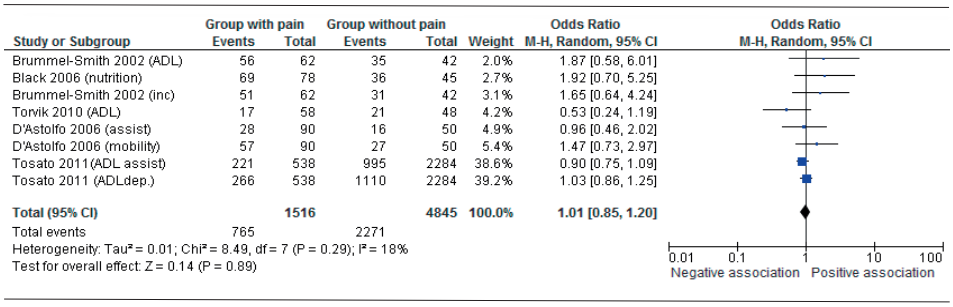
Correlates of pain and ADL or IADL					
First author	***N***	***Pain: prevalence***	***Physical function: prevalence***	***Correlates of pain with ADL or IADL***	***Quality of study***
Brummel-Smith 2002[36]	104 (excluding those unable to self-report pain)	Moderate-severe pain 60%, no-mild pain 40% (50 subject unable to answer)	≥ 1 ADL limitations 92% in dementia sample (n=154)	SOR 1.9 (95% CI: 0.6-6.0) with ≥ 1 ADL limitation	7
Cipher 2004[4]	234	Persistent pain 72%	ADL independency mean 0.09 (SD 0.99)	*Correlations with GMPI 'pain and suffering'* r=-0.04 (α>0.05) with ADL independency	7.5
Shega 2005[44]	115	Any current pain self-report 32%, caregiver report 53%	KATZ mean 8.5 (SD 2.7), IADL mean 15.3 (SD 3.9)	*For self-report pain* No association ADL and IADL (p> 0.05) *For caregiver pain report* No association with ADL or IADL (p> 0.05)	9.5
Shega 2010[45]	5549	Moderate or greater pain: 35.8%	Any IADL impairment: 66.5%	**OR=1.74 (95% CI: 1.15-2.62)** with any iADL impairment (Adjusted for demographics)	9
Torvik 2010[48]	106	Current pain in total group 55%, in cognitive impaired group 52%	Highly or moderate ADL dependent 36%	p=0.20 for current pain and ADL SOR=0.5 (95% CI: 0.2-1.2) for current pain and ADL high/medium v.s. low.	6.5
Tosato 2012[3]	2822	Any pain 19% (moderate/ severe/ excruciating pain 13%)	No disability 8%, assistance required 43%, dependent 49%	SOR 1.0 (95% CI: 0.9-1.2) with ADL-dependent SOR 0.9 (95% CI: 0.75-1.09) with ADL assistance required (Adjusted for age, gender, country, cognitive impairment, number of diseases, ischemic heart disease, stroke, falls, communication problems, and a flare-up of a chronic or recurrent condition)	11.5

Table 6. Correlates of Pain with Physical Function *(continued)*

Correlates of pain and other functional impairment					
First author	***N***	***Pain: prevalence***	***Physical function: prevalence***	***Correlates of pain with other functional impairments***	***Quality of study***
Black 2006 [39]	123	Pain 63%	Nutrition/hydration problems total sample 85%	SOR 1.9 (95% CI: 0.7-5.3) with nutrition/hydration problems	6.5
Brummel-Smith 2002 [40]	104 (excluding those unable to self-report pain)	Moderate-severe pain 60%, no-mild pain 40% (50 subject unable to answer)	≥1 ADL limitations 92% in dementia sample (n=154)	SOR 1.6 (95% CI: 0.6-4.2) with bladder incontinence	7
D'Astolfo 2006 [44]	140	Pain 64% (musculoskeletal pain 40%)	Use of wheel chair 60% Requires assistance 34%	SOR 1.5 (95% CI: 0.7-3.0) with use of wheel chair or bedridden SOR 1.0 (95% CI: 0.5-2.0) with requires assistance (Analyses in sample of no dementia-severe dementia)	7
Lin 2011 [46]	112	Observed pain 37% (PAINAD >=2)	Being restrained 46%; observed care activities: bathing 43%, assisted transfer 31%, self-transfer 26%	**OR=5.4 (95% CI: 2.3-12.5)** and **AOR=3.0 (95% CI: 1.0-8.7)** with being restrained **OR=23.4 (95% CI: 3.0-188)** and **AOR=19.2 (95% CI: 2.3-162)** with bathing **OR=29.7 (95% CI: 3.6-242**) and **AOR=11.3 (95% CI: 1.2-102)** with assisted transfer, both compared to self-transfer (Adjusted for gender, age, wound, restraint, tube present in body, recent fall, severity of dementia and type of activity)	12
Williams 2005[43]	331	Pain 21%, in nh 23%, in rc/al 20% (self-report for subgroup MMSE>10 was higher: 39% and 25%)	Low activity 47%, immobile 12% Low food intake 53% Low fluid intake 51%	OR=0.65 (95% CI: 0.38-1.11) and AOR=0.64 (95% CI: 0.37-1.10) with low activity OR=1.1 (95% CI: 0.49-2.29) and AOR=0.8 (95% CI: 0.37-1.69) with immobility OR=1.18 (95% CI: 0.64-2.17) and AOR=1.03 (95% CI: 0.56-1.87) with low food intake OR=1.20 (95% CI: 0.67-2.15) and AOR 1.14 (95% CI: 0.66-1.99) with low fluid intake (Adjusted for: sex, race, age, cognitive status, number of 10 comorbidities, impairments of 7 activities of daily living)	10

Abbreviations: SOR, Self-Calculated Odds Ratio; ADL, Activities of Daily Living; SD, Standard Deviation; r, correlation coefficient; GMPI, Geriatric Multidimensional Pain and Illness Inventory; PAINAD, Pain Assessment in Advanced Dementia; OR, Odds Ratio; AOR, Adjusted Odds Ratio; KATZ, Index of Independence in Activities of Daily Living; IADL, Instrumental Activities of Daily Living; nh, nursing home; rc/al, residential care/assisted living; MMSE, Mini Mental State Examination

The strongest reported association was with assisted transfer compared to self-transfer; however, this had a very broad confidence interval: OR 29.7 (95% CI 3.6-242)[46]. The remaining eight articles reported associations which were not significant. Based on five articles, the pooled OR (see Figure 4) for pain and overall physical function was 1.01 (95% CI 0.85-1.20).



Note: Studies with a large sample size (e.g., studies using the MDS dataset) were awarded more weight in the meta-analysis. However, this is not necessarily correct because, in observational studies, a larger sample size does not necessarily mean that these studies are of good methodological quality.

Figure 4. Forest plot: Pain and Physical Function (with reports of 5 out of 10 included studies)

Discussion

Despite the increased attention for pain in dementia, relatively few studies have explored associations between pain and NPS, and pain and physical function. We found 22 articles reporting the strength of associations between these three modalities, including only two longitudinal studies.

We found most evidence for the association between pain and depression (in 7 of 11 articles), followed by the association between pain and agitation/aggression (in 5 of 8 articles). The two longitudinal studies reported no direct effects between pain and NPS but only some indirect effects, e.g., of pain through depression. Interestingly, articles reporting a significant positive association between pain and NPS, and between pain and physical function, were mainly of low methodological quality. One article with high methodological quality reported a non-significant correlation between pain frequency and verbal abuse[37]. Four high-quality articles reported a positive association between pain, aggression/agitation and wandering[36 51], between pain and functional impairment[46], and between pain and behavioural symptoms[43].

Due to the hypothesized effect of pain on NPS and physical function, and some overlap of items in the measurement instruments, we expected to find stronger associations; particularly since pain interventions targeting NPS and behavioural interventions targeting pain are reported to reduce both pain and NPS (such as depression and agitation/aggression)[54]. In addition, a cluster RCT by Husebo et al., investigating a sample of moderate to severe dementia patients with challenging behaviour, showed that treating pain led to a significant improvement in mood symptoms such as depression, apathy, and eating

disorders, and improvements in ADL function were also found[12]. Furthermore, research among elderly without cognitive impairment shows an association between pain and depression; there is also evidence that treatment of depression in cognitively intact older patients improves pain and physical function[46 55 56]. It is plausible that this also applies to patients with dementia.

However, the associations found in the present systematic review were rather weak. This may be the result of inadequate assessment of both pain and NPS in the included studies. Most studies did not use measurement instruments developed for the assessment of pain in people with dementia. For example, D'Astolfo et al. did not use a measurement instrument for pain or for NPS, but only screened medical records and found relatively weak and non-significant associations. Also, it is possible that healthcare workers interpret NPS as symptoms of either pain *or* challenging behaviour; if this is the case, then only pain *or* NPS is reported in the medical records and no association will be found.

Five articles used the MDS-RAI Dataset to measure pain and also reported weak associations[3 36 37 50 51]. These articles also report weak associations. This might be due to the doubt about the accuracy of measuring pain in people suffering from dementia with the MDS-RAI Dataset[57 58].

We hypothesize that validated rating scales, used by a professional, will provide a more accurate reflection of the relationship between pain and NPS. This is illustrated by the study of Zieber et al. in which a clear distinction is seen in the strength of the correlations between pain and agitation when rated by a palliative nurse consultant or when rated by the facility nurse[38]. When rated by the palliative nurse consultant the correlation was stronger: $r=0.49$ ($p<0.01$) compared with the rating by the facility nurse: $r=0.28$ ($p<0.05$). This also applied to the correlation between pain and aberrant vocalizations: $r=0.40$ ($p<0.01$) and $r=0.065$ ($p<0.63$), respectively, but not between pain and resisting care: $r=0.51$ ($p<0.01$) and $r=0.48$ ($p<0.01$), respectively. In addition, in a study by Leong et al. a professional used the PAINAD to assess pain and found a SOR of 3.2 (95% CI 1.8-5.9) between pain and depression[35]. However, other studies with a relative strong association between pain and depression did not use professionals or validated rating scales to assess pain in patients with dementia[43 45]. Therefore, the results of the present review cannot fully support the hypothesis of a better reflection of the relationship between pain and NPS when validated rating scales are used by professionals.

Another explanation for the rather weak associations found in this review could be the inclusion of six articles which described individuals with predominantly severe dementia. Together with the progression of dementia, the assessment of pain becomes even more difficult due to diminished pain behaviours[59], but facial expressions tend to increase in the course of dementia[60]. Of the measurement instruments used in the included studies, only the PAINAD and DS-DAT include facial expressions of pain. In addition, in the included studies, the use of antipsychotic drugs could also explain the weak associations. Antipsychotic drugs may distort and diminish the expression of NPS while a possible cause of NPS, for instance pain, is not treated. This may have resulted in the under-recognition and poor report of NPS. However, the study by Ahn et al. shows that, in a subsample of patients without psychotropic drugs, the association between pain and agitation/aggression, and between pain and wandering, was similar to that in residents who used psychotropic drugs[36].

Moreover, we could have anticipated finding rather weak associations, because most of the included studies were cross-sectional in design. This is illustrated by studies that found that a change in pain after an intervention is related to a decrease in NPS or function[61 62]. To some extent the included articles measured overall functional impairment with, for example, total ADL scores. Some articles focused on specific components of physical function, like nutritional status and mobility, which are often hampered in patients with dementia. However, because the focus of these articles was not on the association between pain and physical function, in most cases we had to calculate the association between pain and physical function (SOR) ourselves. This raises the question as to whether physical function is receiving the attention it deserves and, possibly, may even lead to publication bias. Physical inactivity or impairment is an important sign that a patient with dementia could be in pain; this is illustrated by a study in which patients with moderate to severe dementia (treated with acetaminophen) tend to spend more time in social interaction and engage with the environment more actively, than patients who received placebo[62]. Unfortunately, until now, no longitudinal studies are available that describe the course of physical function in patients with dementia in relation to pain.

Strengths and limitations

This study is the first to give a comprehensive and systematic analysis of the associations between pain and NPS, and pain and physical function, in patients with dementia. One of the strengths of this study is that we not only included publications that presented associations between pain and NPS and pain and physical function, but also publications that provide enough information to compute ORs, thus taking full advantage of the available evidence. In addition, when possible, we present the crude OR as this reflects the presence of co-occurrence as perceived by the caregivers. Furthermore, we used a methodological quality assessment based on previously developed checklists[32 33]. By adding extra items focusing on the measurement of pain, study objective and population, we tailored the quality assessment to the purpose of this review. We believe that this strategy has led to a better reflection of the challenges in the assessment of pain and NPS. A possible limitation could be some publication bias, e.g., if some studies do not report the associations because they were negative. Also, we explicitly searched for publications about pain and not for terms like 'distress' or 'discomfort'. However, we believe that this approach provides the best reflection of the complex relation between pain, NPS and physical function. Furthermore, we were unable to include every study in the meta-analysis due to missing data. In addition, the forest plots should be interpreted with caution, since the included studies are heterogeneous and studies with a large sample size (e.g., studies using the MDS Dataset) were awarded more weight in the meta-analysis; however, this weighting is not necessarily justified because, in observational studies, a larger sample size does not necessarily mean that these studies are of good methodological quality. Another possible limitation is that we did not include delirium as a separate search term in our search strategy. However, as delirium is a syndrome with specific neuropsychiatric symptoms, we looked at the clinical features of a delirium by including these symptoms, such as hallucinations and delusions, in our search strategy.

Clinical implications

The American Geriatrics Society (AGS) published clinical guidance on persistent pain, outlining 26 behavioural expressions of pain in the elderly[21]. The AGS panel advises clinicians to assess pain in older persons with moderate to severe dementia via direct observation of this pain-related behaviour, or via history from caregivers. Several observational scales are available based on the presence of or alterations in behaviours, emotions, interactions, and facial expressions. However, there is little empirical evidence that these 26 behavioural expressions are indeed related to pain. In our review, only depression and agitation/aggression seem to be associated with pain.

The advice of direct observation of pain-related behaviour seems to be poorly implemented, as illustrated by this review, in which only three studies used rating scales based on behavioural observations[35 38 46]. It can be assumed that, when this non-optimal situation exists in a research setting, then routine implementation of rating scales based on behavioural observation in clinical practice will be even less optimal.

The results presented in this review do not fully support the association between pain, NPS and functional impairment in dementia. However, they do highlight the presence of difficulties in the management of pain in dementia. This is illustrated by the frequent use of terms like 'behavioural symptoms', 'disruptive behaviour', and 'psychiatric symptoms'. There is no uniform way of reporting neuropsychiatric symptoms; this could complicate the comparison between behavioural symptoms and also reveals the challenges in differentiating between the different, but often very similar, types of challenging behaviour. This also applies to the description of physical function; the specific functions and activities should be properly described (e.g., malnutrition, sleep disturbances, and immobility) and not merely presented as a total ADL score.

Clearly, co-occurrence will not (and can not) be easily observed, probably leading to clinical indecisiveness. However, regardless of co-occurrence, we want to stress the importance of pain detection in patients with dementia because pain can be the cause of other disorders, such as NPS. Moreover, it has been proven that pain treatment significantly reduces behavioural disturbances, such as agitation[12 54 61]. Pain and its consequences have an impact on the quality of life and therefore should be recognized, measured and treated.

Conclusion

This review shows, unexpectedly, rather weak associations between pain and NPS, and between pain and physical function. Nevertheless, the relationship between pain and the onset of NPS, as well as the effect on physical function, remains unclear and should be further explored. To unravel this complex relationship, the course of pain, NPS and physical function should be examined longitudinally, using valid measurement instruments. A longitudinal study design will provide more information on causality and the sequence of these modalities, providing evidence that can be incorporated in clinical practice to improve the management of pain for people with dementia.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

AvD performed the literature searches and selected eligible articles, extracted data from these articles, did the analyses and prepared the first draft of the review. MP contributed to the selection of articles, data extraction and methodological quality assessment of the systematic review. MdW and WA helped to determine the concept of the review and contributed to the writing. All authors reviewed and commented on the report.

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References

1. Feldt KS, Warne MA, Ryden MB. Examining pain in aggressive cognitively impaired older adults. *JGerontolNurs* 1998;24(11):14-22.
2. Zwakhalen SM, Koopmans RT, Geels PJ, et al. The prevalence of pain in nursing home residents with dementia measured using an observational pain scale. *EurJPain* 2009;13(1):89-93. doi: S1090-3801(08)00063-3 [pii];10.1016/j.ejpain.2008.02.009 [doi]
3. Tosato M, Lukas A, van der Roest HG, et al. Association of pain with behavioral and psychiatric symptoms among nursing home residents with cognitive impairment: results from the SHELTER study. *Pain* 2012;153(2):305-10. doi: S0304-3959(11)00593-8 [pii];10.1016/j.pain.2011.10.007 [doi]
4. Cipher DJ, Clifford PA. Dementia, pain, depression, behavioral disturbances, and ADLs: toward a comprehensive conceptualization of quality of life in long-term care. *IntJGeriatrPsychiatry* 2004;19(8):741-48. doi: 10.1002/gps.1155 [doi]
5. Buffum MD, Miaskowski C, Sands L, et al. A pilot study of the relationship between discomfort and agitation in patients with dementia. *GeriatrNurs* 2001;22(2):80-85. doi: S0197-4572(01)55458-0 [pii];10.1067/mgn.2001.115196 [doi]
6. Geda YE, Schneider LS, Gitlin LN, et al. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *AlzheimersDement* 2013;9(5):602-08. doi: S1552-5260(12)02570-8 [pii];10.1016/j.jalz.2012.12.001 [doi]
7. Ballard C, Bannister C, Solis M, et al. The prevalence, associations and symptoms of depression amongst dementia sufferers. *JAffectDisord* 1996;36(3-4):135-44.
8. Bartels SJ, Horn SD, Smout RJ, et al. Agitation and depression in frail nursing home elderly patients with dementia: treatment characteristics and service use. *AmJGeriatrPsychiatry* 2003;11(2):231-38.
9. Zuidema S, Koopmans R, Verhey F. Prevalence and predictors of neuropsychiatric symptoms in cognitively impaired nursing home patients. *JGeriatrPsychiatry Neurol* 2007;20(1):41-49. doi: 20/1/41 [pii];10.1177/0891988706292762 [doi]
10. Heeren O, Borin L, Raskin A, et al. Association of depression with agitation in elderly nursing home residents. *JGeriatrPsychiatry Neurol* 2003;16(1):4-7.
11. Lyketsos CG, Colenda CC, Beck C, et al. Position statement of the American Association for Geriatric Psychiatry regarding principles of care for patients with dementia resulting from Alzheimer disease. *AmJGeriatrPsychiatry* 2006;14(7):561-72. doi: 14/7/561 [pii];10.1097/01.JGP.0000221334.65330.55 [doi]
12. Husebo BS, Ballard C, Fritze F, et al. Efficacy of pain treatment on mood syndrome in patients with dementia: a randomized clinical trial. *International Journal of Geriatric Psychiatry* 2013;29(2) doi: doi: 10.1002/gps.4063
13. Won A, Lapane K, Gambassi G, et al. Correlates and management of nonmalignant pain in the nursing home. SAGE Study Group. Systematic Assessment of Geriatric drug use via Epidemiology. *JAmGeriatrSoc* 1999;47(8):936-42.
14. Beullens J, Schols J. [Treatment of insomnia in demented nursing home patients: a review]. *TijdschrGerontolGeriatr* 2002;33(1):15-20.
15. Giron MS, Forsell Y, Bernsten C, et al. Sleep problems in a very old population: drug use and clinical correlates. *JGerontolA BiolSciMedSci* 2002;57(4):M236-M40.

16. Plooij B, Scherder EJ, Eggermont LH. Physical inactivity in aging and dementia: a review of its relationship to pain. *JClinNurs* 2012;21(21-22):3002-08. doi: 10.1111/j.1365-2702.2011.03856.x [doi]
17. Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol* 2003;2(11):677-86. doi: S1474442203005568 [pii]
18. Achterberg WP, Scherder E, Pot AM, et al. Cardiovascular risk factors in cognitively impaired nursing home patients: a relationship with pain? *EurJPain* 2007;11(6):707-10. doi: S1090-3801(06)00171-6 [pii];10.1016/j.ejpain.2006.10.006 [doi]
19. Nygaard HA, Jarland M. Are nursing home patients with dementia diagnosis at increased risk for inadequate pain treatment? *International Journal of Geriatric Psychiatry* 2005;20(8):730-37.
20. Tait RC, Chibnall JT. Under-Treatment of Pain in Dementia: Assessment is Key. *Journal of the American Medical Directors Association* 2008;9(6):372-74.
21. AGS PoPPiOP. The management of persistent pain in older persons. *JAmGeriatrSoc* 2002;50(6 Suppl):S205-S24. doi: jgs5071 [pii]
22. Achterberg WP, Pieper MJ, van Dalen-Kok AH, et al. Pain management in patients with dementia. *ClinIntervAging* 2013;8:1471-82. doi: 10.2147/CIA.S36739 [doi];cia-8-1471 [pii]
23. Corbett A, Husebo B, Malcangio M, et al. Assessment and treatment of pain in people with dementia. *NatRevNeurol* 2012;8(5):264-74. doi: nrneurol.2012.53 [pii];10.1038/nrneurol.2012.53 [doi]
24. Zwakhalen SM, Hamers JP, Abu-Saad HH, et al. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatr* 2006;6:3. doi: 10.1186/1471-2318-6-3
25. Husebo BS, Ostelo R, Strand LI. The MOBID-2 pain scale: Reliability and responsiveness to pain in patients with dementia. *EurJPain* 2014 doi: 10.1002/ejp.507 [doi]
26. Husebo BS, Corbett A. Dementia: Pain management in dementia-the value of proxy measures. *NatRevNeurol* 2014 doi: nrneurol.2014.66 [pii];10.1038/nrneurol.2014.66 [doi]
27. Briesacher BA, Limcangco MR, Simoni-Wastila L, et al. The quality of antipsychotic drug prescribing in nursing homes. *ArchInternMed* 2005;165(11):1280-85. doi: 165/11/1280 [pii];10.1001/archinte.165.11.1280 [doi]
28. Advisory. FPH. Deaths with antipsychotics in elderly patients with with behavioral disturbances., 2005.
29. Desai VC, Heaton PC, Kelton CM. Impact of the Food and Drug Administration's antipsychotic black box warning on psychotropic drug prescribing in elderly patients with dementia in outpatient and office-based settings. *AlzheimersDement* 2012;8(5):453-57. doi: S1552-5260(11)02717-8 [pii];10.1016/j.jalz.2011.08.004 [doi]
30. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine* 2009;151(4):264-69.
31. Reisberg B, Ferris SH, de Leon MJ, et al. The Global Deterioration Scale for assessment of primary degenerative dementia. *Am J Psychiatry* 1982;139(9):1136-9.
32. van der Windt DA, Zeegers MP, Kemper HC, et al. [Practice of systematic reviews. VI. Searching, selection and methodological evaluation of etiological research]. *NedTijdschrGeneeskd* 2000;144(25):1210-14.

33. van der Windt DA, Thomas E, Pope DP, et al. Occupational risk factors for shoulder pain: a systematic review. *OccupEnvironMed* 2000;57(7):433-42.
34. Kunik ME, Cully JA, Snow AL, et al. Treatable comorbid conditions and use of VA health care services among patients with dementia. *PsychiatrServ* 2005;56(1):70-75. doi: 56/1/70 [pii];10.1176/appi.ps.56.1.70 [doi]
35. Leong IY, Nuo TH. Prevalence of pain in nursing home residents with different cognitive and communicative abilities. *ClinJPain* 2007;23(2):119-27. doi: 10.1097/01.ajp.0000210951.01503.3b [doi];00002508-200702000-00002 [pii]
36. Ahn H, Horgas A. The relationship between pain and disruptive behaviors in nursing home resident with dementia. *BMCGeriatr* 2013;13:14. doi: 1471-2318-13-14 [pii];10.1186/1471-2318-13-14 [doi]
37. Volicer L, Van der Steen JT, Frijters DH. Modifiable factors related to abusive behaviors in nursing home residents with dementia. *JAmMedDirAssoc* 2009;10(9):617-22. doi: S1525-8610(09)00240-0 [pii];10.1016/j.jamda.2009.06.004 [doi]
38. Zieber CG, Hagen B, Armstrong-Esther C, et al. Pain and agitation in long-term care residents with dementia: use of the Pittsburgh Agitation Scale. *IntJPalliatNurs* 2005;11(2):71-78.
39. Black BS, Finucane T, Baker A, et al. Health problems and correlates of pain in nursing home residents with advanced dementia. *Alzheimer Disease & Associated Disorders* 2006;20(4):283-90.
40. Brummel-Smith K, London MR, Drew N, et al. Outcomes of pain in frail older adults with dementia. *JAmGeriatrSoc* 2002;50(11):1847-51. doi: jgs50514 [pii]
41. Cipher DJ, Clifford PA, Roper KD. Behavioral manifestations of pain in the demented elderly. *JAmMedDirAssoc* 2006;7(6):355-65. doi: S1525-8610(05)00645-6 [pii];10.1016/j.jamda.2005.11.012 [doi]
42. Norton MJ, Allen RS, Snow AL, et al. Predictors of need-driven behaviors in nursing home residents with dementia and associated certified nursing assistant burden. *Aging MentHealth* 2010;14(3):303-09. doi: 921676875 [pii];10.1080/13607860903167879 [doi]
43. Williams CS, Zimmerman S, Sloane PD, et al. Characteristics associated with pain in long-term care residents with dementia. *Gerontologist* 2005;45(1):68-73.
44. D'Astolfo CJ, Humphreys BK. A record review of reported musculoskeletal pain in an Ontario long term care facility. *BMCGeriatr* 2006;6:5. doi: 1471-2318-6-5 [pii];10.1186/1471-2318-6-5 [doi]
45. Gruber-Baldini AL, Zimmerman S, Boustani M, et al. Characteristics associated with depression in long-term care residents with dementia. *Gerontologist* 2005;45 Spec No 1(1):50-55. doi: 45/suppl_1/50 [pii]
46. Lin PC, Lin LC, Shyu YIL, et al. Predictors of pain in nursing home residents with dementia: a cross-sectional study. *Journal of Clinical Nursing* 2011;20(13-14):1849-57.
47. Morgan RO, Sail KR, Snow AL, et al. Modeling Causes of Aggressive Behavior in Patients With Dementia. *Gerontologist* 2012 doi: gns129 [pii];10.1093/geront/gns129 [doi]
48. Shega JW, Hougham GW, Stocking CB, et al. Factors associated with self- and caregiver report of pain among community-dwelling persons with dementia. *JPalliatMed* 2005;8(3):567-75. doi: 10.1089/jpm.2005.8.567 [doi]
49. Shega JW, Ersek M, Herr K, et al. The multidimensional experience of noncancer pain: does cognitive status matter? *Pain Med* 2010;11(11):1680-87. doi: 10.1111/j.1526-4637.2010.00987.x [doi]

50. Leonard R, Tinetti ME, Allore HG, et al. Potentially modifiable resident characteristics that are associated with physical or verbal aggression among nursing home residents with dementia. *ArchInternMed* 2006;166(12):1295-300. doi: 166/12/1295 [pii];10.1001/archinte.166.12.1295 [doi]
51. Volicer L, Frijters DH, Van der Steen JT. Relationship between symptoms of depression and agitation in nursing home residents with dementia. *IntJGeriatrPsychiatry* 2011 doi: 10.1002/gps.2800 [doi]
52. Torvik K, Kaasa S, Kirkevold O, et al. Pain and quality of life among residents of Norwegian nursing homes. *Pain ManagNurs* 2010;11(1):35-44. doi: S1524-9042(09)00020-4 [pii];10.1016/j.pmn.2009.01.001 [doi]
53. Volicer L, Krsiak M. Assessment and measurement of pain in patients with advanced dementia. [Czech]. *Bolest* 2006;9(1):8-13.
54. Pieper MJ, van Dalen-Kok AH, Francke AL, et al. Interventions targeting pain or behaviour in dementia: A systematic review. *Ageing ResRev* 2013 doi: S1568-1637(13)00024-X [pii];10.1016/j.arr.2013.05.002 [doi]
55. Smalbrugge M, Jongenelis LK, Pot AM, et al. Pain among nursing home patients in the Netherlands: prevalence, course, clinical correlates, recognition and analgesic treatment--an observational cohort study. *BMCGeriatr* 2007;7:3. doi: 1471-2318-7-3 [pii];10.1186/1471-2318-7-3 [doi]
56. Landi F, Onder G, Cesari M, et al. Pain and its relation to depressive symptoms in frail older people living in the community: an observational study. *JPain SymptomManage* 2005;29(3):255-62. doi: S0885-3924(04)00570-6 [pii];10.1016/j.jpainsymman.2004.06.016 [doi]
57. Lukas A, Mayer B, Fialova D, et al. Pain Characteristics and Pain Control in European Nursing Homes: Cross-sectional and Longitudinal Results From the Services and Health for Elderly in Long TERm care (SHELTER) Study. *JAmMedDirAssoc* 2013 doi: S1525-8610(12)00464-1 [pii];10.1016/j.jamda.2012.12.010 [doi]
58. Fisher SE, Burgio LD, Thorn BE, et al. Pain assessment and management in cognitively impaired nursing home residents: association of certified nursing assistant pain report, Minimum Data Set pain report, and analgesic medication use. *JAmGeriatrSoc* 2002;50(1):152-56. doi: 50021 [pii]
59. Monroe TB, Gore JC, Chen LM, et al. Pain in people with Alzheimer disease: Potential applications for psychophysical and neurophysiological research. *Journal of Geriatric Psychiatry and Neurology* 2012;25(4):240-55.
60. Kunz M, Scharmann S, Hemmeter U, et al. The facial expression of pain in patients with dementia. *Pain* 2007;133(1-3):221-28. doi: S0304-3959(07)00516-7 [pii];10.1016/j.pain.2007.09.007 [doi]
61. Husebo B, Ballard C, Sandvik R, et al. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. *BMJ: British Medical Journal (Overseas & Retired Doctors Edition)* 2011;343(7816):193-93.
62. Chibnall JT, Tait RC, Harman B, et al. Effect of acetaminophen on behavior, well-being, and psychotropic medication use in nursing home residents with moderate-to-severe dementia. *JAmGeriatrSoc* 2005;53(11):1921-29. doi: JGS53572 [pii];10.1111/j.1532-5415.2005.53572.x [doi]

Appendix 1 Search terms

Dementia	"Dementia"[mesh:noexp] OR "Alzheimer Disease"[mesh] OR "Frontotemporal Lobar Degeneration"[mesh:noexp] OR "Lewy Body Disease"[mesh] OR dementia[tw] OR dement*[tw] OR alzheimer*[tw] OR "Frontotemporal Lobar Degeneration" OR "Lewy Body Disease" OR "Delirium, Dementia, Amnestic, Cognitive Disorders"[Mesh:NoExp]
Pain	pain OR pain* OR "Analgesics"[mesh] OR Analgesic[tw] OR Analgesics[tw] OR discomfort[tw] OR discomfort*
Depression	"Depressive Disorder"[mesh] OR depression[tw] OR depressive[tw] OR "Depression"[mesh]
BPSD	agitation OR agitated OR "Psychomotor Agitation"[mesh] OR "Psychomotor Hyperactivity" OR Restlessness OR "Psychomotor Excitement" OR "Psychomotor Disorders"[mesh:noexp] OR "behavioural disturbance" OR "behavioural disturbances" OR "behavioural disturbance" OR "behavioural disturbances" OR "Social Behaviour Disorders"[mesh] OR "dysfunctional behaviour" OR "dysfunctional behaviours" OR "dysfunctional behaviour" OR "dysfunctional behaviours" OR "challenging behaviour" OR "challenging behaviours" OR "challenging behaviour" OR "challenging behaviours" OR BPSD[tw] OR "behavioural and psychological symptoms of dementia" OR "behavioural and psychological symptoms of dementia" OR hallucination OR hallucinations OR aggression OR aggressive behaviour OR aggressive behaviour OR apathy OR delusion OR delusions OR delusional OR resistiveness OR "Behavioural Symptoms"[mesh:noexp] OR "psychological symptoms"[tiab] OR "psychological symptom"[tiab] OR "Behavioural Symptoms"[tiab] OR "Behavioural Symptom"[tiab] OR "Behavioural Symptoms"[tiab] OR "Behavioural Symptom"[tiab] OR "neuropsychiatric symptom"[tiab] OR "neuropsychiatric symptoms"[tiab] OR irritability OR irritabilities OR "anxiety"[mesh:noexp] OR "anxiety disorders"[mesh] OR "anxiety disorder" OR "anxiety disorders" OR anxiety[ti]
Mobility	"mobility" OR "Mobility Limitation"[mesh] OR "Range of Motion, Articular"[Mesh] OR "Motor Activity"[Mesh]
Sleep	"sleep"[Mesh] OR "sleep disorder" OR "sleep disorders" OR "Sleep Disorders"[Mesh] OR "sleep deprivation" OR "Sleep Deprivation"[Mesh] OR "circadian rhythm" OR "Circadian Rhythm"[Mesh] OR "Circadian Clocks"[Mesh] OR "sleeping"
Eating	"eating"[Mesh] OR "eating disorder" OR "eating disorders" OR "eating disorders"[Mesh] OR eating[ti]
ADL	"ADL" OR "activities of daily living"[Mesh] OR "activities of daily living" OR "functional impairment" OR "functional status" OR "functional ability" OR "functional abilities" OR "functional outcome" OR "functional outcomes" OR functional[ti] OR "physical functioning" OR "physical function" OR "physical functions" OR functioning[ti] OR barthel[tiab] OR katz[tiab]

Appendix 1.2 Prisma 2009 checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not applicable
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Additional file 1 and page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Appendix 1.2 Prisma 2009 checklist *(continued)*

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Not applicable
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 and figure 1 on page 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Additional file 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 3-6, additional file 'Figures'
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Additional file 'Figures' and pages 12-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Not applicable
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14-15-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org.

Appendix 2 Rating scales for pain that were used in the reported studies

Pain rating scale	Type of measurement	Reason for development	Studies (first author)	
Rating of observations				
PAINAD	Pain Assessment in Advanced Dementia Scale (Warden 2003)	5-item scale (nonverbal behaviours) Each item rated on a 3-point scale (0-2)	Developed to provide a clinically relevant and easy to use pain assessment tool for individuals with advanced dementia	Leong 2007, Lin 2011
DS-DAT	Discomfort Scale-Dementia Alzheimer Type (Hurley 1992)	9-item scale (nonverbal behaviours) Each item is measured for absence or presence of indicators of *discomfort* which, if present, are scored for frequency, duration and intensity·	Developed to measure *discomfort* in elders with dementia of the Alzheimer's type·	Zieber 2005
Rating of pain based on interview or observation				
GMPI	Geriatric Multidimensional Pain and Illness Inventory (Clifford 2005)	12-items in 3 subscales: pain and suffering (3), interference (5), emotional distress (4) Each item rated on a 10-point scale	Designed to assess pain and its functional, social and emotional consequences, in residents in long term care	Cipher 2004/2006
PPQ	Proxy Pain Questionnaire (Fisher 2002)	3 items: presence Y/N, frequency, and intensity of pain on 13-point scale	To assess pain in cognitively impaired older people	Norton 2010 (1 item)
PGC-PIS	Philadelphia Geriatric Centre–Pain Intensity Scale (Parmelee 1991)	"worst pain" item: highest level of pain experienced over preceding 4 weeks on a 5-point scale		Gruber-Baldini 2005, Kunik 2005/ Morgan 2012, Williams 2005
InterRAI LCTF	InterRAI instrument for Long-Term Care Facilities	Any type of pain or discomfort in 3 days before assessment, based on extensive evaluation Items on pain frequency, and severity (0-4)		Tosato 2011

Appendix 2 Rating scales for pain that were used in the reported studies *(continued)*

Pain rating scale	Type of measurement	Reason for development	Studies (first author)
MDS **Self-report of pain***	Minimum Data Set	Items: pain intensity and frequency Each item rated on a 3-point scale (0-3)	Ahn 2013, Leonard 2006, Volicer 2009/2011
- VDS VRS	Non-verbal visual analogue scale Verbal Descriptor Scale Verbal Rating Scale	7-point scale 7-point scale, pain right now 4-point scale, pain right now	Brummel-Smith 2002 Shega 2005/2010 Torvik 2010

* Developed for self-report, but sometimes used in interview

References

1 Clifford, P.A. and Cipher, D.J., 2008. The Geriatric Mulitdimensional Pain and Illness Inventory : A New Instrument Assessing Pain and Illness in Long-Term Care. Clinical Gerontologist 28, 45-61.

2 Fisher, S.E., Burgio, L.D., Thorn, B.E., Allen-Burge, R., Gerstle, J., Roth, D.L., and Allen, S.J., 2002. Pain assessment and management in cognitively impaired nursing home residents: association of certified nursing assistant pain report, Minimum Data Set pain report, and analgesic medication use. J.Am.Geriatr.Soc. 50, 152-156.

3 Hurley, A.C., Volicer, B.J., Hanrahan, P.A., Houde, S., and Volicer, L., 1992. Assessment of discomfort in advanced Alzheimer patients. Res.Nurs.Health 15, 369-377.

4 Parmelee, P.A., Katz, I.R., and Lawton, M.P., 1991. The relation of pain to depression among institutionalized aged. J.Gerontol. 46, 15-21.

5 Warden, V., Hurley, A.C., and Volicer, L., 2003. Development and psychometric evaluation of the Pain Assessment in Advanced Dementia (PAINAD) scale. J.Am.Med.Dir.Assoc. 4, 9-15.

Appendix 3 Quality assessment of included studies

Author	Morgan[43]	Volicer[47]	Ahn[32]	Bartels[8]	Black[35]	Brummel-Smith[36]
Year	2021	2011	2003	2003	2006	2002
Journal	Gerontologist	Int J Geriatr Psychiatry	BMC Geriatrics	Am J Geriatr Psychiatry	Alzheimer Dis&Ass Dis	J Am Geriatr Soc
Study population						
Is there a specific, clearly stated objective described?	1	1	1	1	1	1
Is the stated objective similar to our objective?	0	1	1	0	1	0
Study population						
Were valid selection criteria used for the study population? (sampling frame and distribution of the population by age and sex)	1	1	1	1	1	1
Is there a specified selected population? (other than severity of dementia and age) For example, a population selected on pain (e.g., pressure ulcers), behaviour or function. (yes=o, no=1)	0	1	1	0	0	0
Did more than 80% of the eligible subjects participate in the study? Or did 60-80% participate and non-responders were not selective? (data presented)	1	1	1	1	0	1
Is there major and selective loss during follow-up? (yes=0, no=1)	1	1				
Measurement of pain			1	0	0	0.5
Was pain measured with a valid measurement instrument? (rating of observations (2), rating based on observations (1), self-report instruments (0,5) no measurement instrument (0))	1	1	0.5	0	0.5	0.5
Was the method of detection by direct observation (1), interview staff/ proxy/self-report (0,5) or screening medical records (0)?	0.5	1.5	0.5	0	0	1
Was the measurement performed by a trained professional/research assistant (1), staff member (0,5) or a proxy/self-report (0)?	0	0.5				
Outcome measure (behaviour, physical function)			1	1	1	1
Was the outcome measured with a valid and reproducible method?	1	1				
Was the follow-up period sufficient enough?	1	1	1	0	1	1
Analysis			1	0	1	0
Were the results adjusted for possible confounders?	1	0	10	4	6.5	7
Is there an association presented (OR/RR/correlation coefficient), including 95% CIs and numbers in the analyses?	1	1				
Total score	9.5	12				

Appendix 3 Quality assessment of included studies *(continued)*

Author	Cipher[4]	Cipher[37]	D'Astolfo[40]	Gruber-Baldini[41]	Kunik[30]	Leonard[46]
Year	2004	2006	2006	2006	2005	2006
Journal	Int J Geriatr Psychiatry	J Am Med Dir Assoc	BMC Geriatrics	Gerontologist	Psychiatr Serv	Arch Intern Med
Study population						
Is there a specific, clearly stated objective described?	1	1	1	1	1	1
Is the stated objective similar to our objective?	0	1	1	0	1	1
Study population						
Were valid selection criteria used for the study population? (sampling frame and distribution of the population by age and sex)	1	1	1	1	1	1
Is there a specified selected population? (other than severity of dementia and age) For example, a population selected on pain (e.g. pressure ulcers), behaviour or function. (yes=o, no=1)	0	0	1	1	1	1
Did more than 80% of the eligible subjects participate in the study? Or did 60-80% participate and non-responders were not selective? (data presented)	1	0	1	1	0	1
Measurement of pain						
Was pain measured with a valid measurement instrument? (rating of observations (2), rating based on observations (1), self-report instruments (0,5) no measurement instrument (0))	1	1	0	1	1	1
Was the method of detection by direct observation (1), interview staff/proxy/self-report (0,5) or screening medical records (0)?	0.5	0.5	0	0	0.5	0
Was the measurement performed by a trained professional/research assistant (1), staff member (0,5) or a proxy/self-report (0)?	1	1	0	0.5	1	0
Outcome measure (behaviour, physical function)						
Was the outcome measured with a valid and reproducible method?	1	1	1	1	1	1
Analysis						
Were the results adjusted for possible confounders?	0	0	1	1	0	1
Is there an association presented (OR/RR/correlation coefficient), including 95% CIs and numbers in the analyses?	1	1	0	1	1	1
Total score	7.5	7.5	7	8.5	8.5	9

Appendix 3 Quality assessment of included studies *(continued)*

Author	Leong[31]	Lin[42]	Norton[43]	Shega[44]	Shega[45]	Torvik[48]
Year	2007	2011	2010	2005	2010	2010
Journal	Clin J Pain	Journal of Clinical Nurs	Gerontologist	J Palliat Med	Pain Med	Pain Manag Nurs
Study population						
Is there a specific, clearly stated objective described?	1	1	1	1	1	1
Is the stated objective similar to our objective?	0	1	1	1	0	0
Study population						
Were valid selection criteria used for the study population? (sampling frame and distribution of the population by age and sex)	1	1	1	1	1	1
Is there a specified selected population? (other than severity of dementia and age) For example, a population selected on pain (e.g., pressure ulcers), behaviour or function. (yes=o, no=1)	1	1	0	1	1	0
Did more than 80% of the eligible subjects participate in the study? Or did 60-80% participate and non-responders were not selective? (data presented)	1	1	1	1	1	0
Measurement of pain						
Was pain measured with a valid measurement instrument? (rating of observations (2), rating based on observations (1), self-report instruments (0,5) no measurement instrument (0))	2	2	1	1	0.5	1
Was the method of detection by direct observation (1), interview staff/ proxy/self-report (0,5) or screening medical records (0)?	0.5	1	0.5	0.5	0.5	0.5
Was the measurement performed by a trained professional/research assistant (1), staff member (0,5) or a proxy/self-report (0)?	1	1	0.5	1	1	1
Outcome measure (behaviour, physical function)						
Was the outcome measured with a valid and reproducible method?	1	1	1	1	1	1
Analysis						
Were the results adjusted for possible confounders?	0	1	1	0	1	0
Is there an association presented (OR/RR/correlation coefficient), including 95% CIs and numbers in the analyses?	0	1	1	1	1	1
Total score	8.5	12	9	9.5	9	6.5

Appendix 3 Quality assessment of included studies *(continued)*

Author	Tosato[3]	Volicer[33]	Williams[39]	Zieber[34]
Year	2012	2009	2005	2005
Journal	Pain	J Am Med Dir Assoc	Gerontologist	Int J Palliat Nurs
Study population				
Is there a specific, clearly stated objective described?	1	1	1	1
Is the stated objective similar to our objective?	1	1	1	1
Study population				
Were valid selection criteria used for the study population? (sampling frame and distribution of the population by age and sex)	1	1	1	1
Is there a specified selected population? (other than severity of dementia and age) For example, a population selected on pain (e.g. pressure ulcers), behaviour or function.(yes=o, no=1)	1	1	1	0
Did more than 80% of the eligible subjects participate in the study? Or did 60-80% participate and non-responders were not selective? (data presented)	1	1	1	0
Measurement of pain				
Was pain measured with a valid measurement instrument? (rating of observations (2), rating based on observations (1), self-report instruments (0,5) no measurement instrument (0))	1	1	1	2
Was the method of detection by direct observation (1), interview staff/ proxy/self-report (0,5) or screening medical records (0)?	0.5	1	0.5	1
Was the measurement performed by a trained professional/research assistant (1), staff member (0,5) or a proxy/self-report (0)?	1	0	0.5	1
Outcome measure (behaviour, physical function)				
Was the outcome measured with a valid and reproducible method?	1	1	1	0
Analysis				
Were the results adjusted for possible confounders?	1	1	1	0
Is there an association presented (OR/RR/correlation coefficient), including 95% CIs and numbers in the analyses?	1	1	1	1
Total score	11.5	11	10	8