

# Is pain sensitivity altered in people with Alzheimer's disease? A systematic review and meta-analysis of experimental pain research

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## **Background**

Clinical studies suggest people with Alzheimer's disease (AD) have altered pain sensitivity. Experimental pain research is equivocal.

## **Objective**

Conduct a meta-analysis to investigate if people with AD have altered pain sensitivity compared to healthy controls (HCs).

## **Methods**

Three authors searched electronic databases from inception till November 2015 for experimental pain studies in AD vs. HCs. Outcome measures were pain threshold, tolerance, pain ratings, heart rate response to noxious stimuli and the Facial Action Coding System (FACS). Random effect meta-analysis calculating Hedges'  $g \pm 95\%$  confidence intervals (CI) was conducted.

## **Results**

Thirteen studies were identified, including 256 people with AD (74.6 ( $\pm 5.6$ ) years, 59% females with a mean mini mental state examination (MMSE) score of 19.2) and 260 HCs. Meta-analysis demonstrated no significant difference in pain threshold ( $g=0.025$ , 95% CI -0.315-0.363,  $p=0.88$ ,  $n_{AD}=135$ ,  $n_{HCs}=157$ ), pain tolerance ( $g=-0.363$ , 95% CI -2.035-1.309,  $p=0.67$ ,  $n_{AD}=41$ ,  $n_{HCs}=53$ ) or pain intensity ratings ( $g=0.03$ ,  $p=0.89$ ,  $n_{AD}=138$ ,  $n_{HCs}=135$ ). Heart rate response to pain was less pronounced in AD but not significant ( $g=-0.746$ ,  $p=0.11$ ). People with AD ( $n=90$ ) had significantly higher FACS scores versus HCs ( $n=109$ ) ( $g=0.442$ ,  $p=0.03$ ) indicating increased pain. Meta-regression demonstrated that an increasing percentage of AD female participants moderated pain threshold ( $p=0.02$ ) whilst MMSE scores did not ( $p=0.19$ ).

## **Conclusion**

People with AD have a greater sensitivity to pain when validated observer ratings of facial expressions are used. Verbal response to painful stimuli, even under experimental conditions, may mean pain is not identified in people with AD. Clinically useful observer rated pain tools may be the most appropriate way to assess pain in AD.

**Key words:** Alzheimer's disease; dementia pain; experimental pain; meta-analysis; systematic review

## 1.1 Introduction

There is an increasing emphasis on the timely identification and management of pain among people with dementia, with prevalence estimates ranging between 50 and 93% [1-3]. Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 60% of cases [4]. In addition to changes in the transentorhinal cortex and hippocampus regions that occur with AD [5], neurodegenerative changes in the medial thalamic nuclei, hypothalamus, cingulate and insular cortex have been identified [6]. These areas are key components of the medial pain system, which is integral to the processing of the affective-motivational dimension of pain [7,8]. Interestingly, the areas of the brain that comprise the lateral pain system, which are related to the sensory-discriminative dimension (location, sensory quality and intensity) of pain appear to be relatively unaffected in AD [6]. Collectively, these findings suggest that the way pain is appraised as well as the emotional component of pain (e.g. distress) may be particularly affected in AD. Moreover, people with AD experience considerable deteriorations in their cognitive ability, making the identification and communication of pain for the individuals affected and healthcare staff challenging [9].

These inherent challenges of accurately assessing the prevalence of pain among people with AD, may mean that current prevalence rates are greatly underestimated [9]. Nonetheless, it is essential that pain is identified and appropriately managed among people with dementia, since undetected pain has been associated with functional decline [10], falls [11] and greater behavioural and psychiatric symptoms of dementia (BPSD) such as agitation [12,13]. Despite the fact that people with dementia seem to have a higher prevalence of pain than matched healthy controls (HCs), some evidence suggests that pain is undertreated in this group [14,15]; although a recent study among nursing home residents has suggested this may not be the case [16].

Understanding if pain sensitivity is altered in AD is important to inform the clinical assessment and management of pain in this group. Experimental pain testing methods circumvent some of the concerns attributed with pain data collected among people with AD in clinical settings. Noxious stimulation can be precisely controlled, and the laboratory setting facilitates the assessment of pain using observer ratings or self-report ratings and stimulus-dependent or physiological measures including pain threshold, pain tolerance and heart rate response. Given that some of these measures rely more heavily on verbal communication and intact cognitive processing than others, it is important to consider a range of assessment measures when examining pain sensitivity in AD, given that this type of impairment is an important feature of the condition[17].

A previous narrative review [18] of the experimental pain literature in AD concluded that the research is equivocal but proposed that pain sensitivity does not appear to be reduced in AD versus HCs. Whilst this narrative review, conducted by experts in the field, was helpful and advanced the field, some pertinent questions remain unanswered. For instance, no meta-analysis has been undertaken, a technique which enables the logical pooling of studies which can provide a more accurate oversight of any outcome as opposed to considering individual studies in isolation [19]. In addition, it remains unclear how the pain experience of people with AD is influenced by different assessment methods, dimensions and patient characteristics (e.g. age, gender and cognition). Meta-regression can help disentangle the influence of important moderators.

The aim of the current paper was to conduct a comprehensive systematic review and meta-analysis comparing AD and HCs participant's response to experimentally induced pain. Specific aims are to: (1) examine whether AD and HCs differ in sensitivity to experimentally-induced pain; (2) examine whether pain sensitivity is altered according to the method of pain assessment, including pain threshold, pain tolerance, self-reported pain ratings, physiological

response to painful stimuli and the observer rated Facial Action Coding System (FACS, [20]);

(3) conduct meta regression investigating the influence of potentially important moderating variables (e.g. age, cognitive status).

## **2.1 Method**

This systematic review was conducted in accordance with the MOOSE guidelines [21] and the PRISMA statement [22].

### *2.2 Eligibility criteria*

Studies were selected for inclusion that utilised: (1) A group with AD, diagnosed according to recognized clinical assessments (e.g. DSM, ICD) and meeting the NINCDS-ADRDA Alzheimer's Criteria [23]; (2) A comparison control group of healthy individuals without any known cognitive impairment; (3) An experimental pain stimulus and at least one of the following established pain response measures: pain threshold, pain tolerance, pain ratings, physiological response to painful stimuli (e.g. heart rate changes) and observer-rated facial assessments of pain response (e.g. FACS).

Studies were excluded if participants' AD or cognitive status was determined solely with a screening tool (e.g. mini mental state examination, MMSE [24]). We did not exclude any studies based on study setting. Although we searched for articles in any language, only articles published in English and Italian were automatically included (languages spoken by the review team). However, if we encountered studies in other languages, we contacted the primary authors three times over a month to acquire and clarify the data in order to maximise the studies included within our review.

### *2.3 Information sources and search details*

Three independent reviewers (BS, TT, MS) performed electronic database searches using EMBASE (1974 to present), MEDLINE (1946 to present) and PsycINFO (1967 to present), with the final search performed on 1<sup>st</sup> November, 2015. The search terms used were (dementia OR Alzheimer's disease OR cognitively impaired) AND (pain sensitivity OR pain threshold OR pain

tolerance OR pain perception). The reference lists of all included studies and recent review papers [18] studies were also considered for potentially relevant articles.

#### *2.4 Study selection*

After removal of duplicates, two reviewers (BS, NV) screened titles and abstracts for potential eligibility, and developed a list of full text articles through consensus. Two authors (TT, BS) considered the full texts of included articles and a final list of eligible articles was agreed. We contacted corresponding/first authors up to 3 times over a month to clarify study eligibility and/or acquire additional data.

#### *2.5 Outcomes*

Primary outcome assessments were: (1) pain threshold (the point at which pain is first perceived), (2) pain tolerance (the point at which pain can no longer be tolerated), (3) pain ratings of intensity/affect, (4) physiological response to painful stimuli (heart rate response) and (5) FACS scores.

#### *2.6 Data Extraction*

Study data were extracted independently by two authors (TT, NV) with details recorded for pain induction method (modality, body side), pain assessment outcome, AD participant (demographics, diagnostic method, symptom severity, medication) and HC group (demographics) details, study design and geographical location. We recorded group means and standard deviations for each pain measure, or any other available information that would allow computation of effect size (see 'Meta-Analysis' section below).

### *2.7 Methodological study appraisal*

Two authors independently completed methodological quality assessment of included articles using the Newcastle Ottawa Scale or NOS [25]. If any disagreement arose, a third author was available for mediation. The NOS provides an assessment of the methodological quality of non-randomised trials and its content validity and reliability have been established [25]. Included studies are judged on 9 items across three key areas: selection of the participants, comparability of the participants and outcomes. Each study receives an overall score for methodological quality of up to 9 points (one for each item) and scores of 5 and above are considered to reflect satisfactory study quality [25].

### *2.8 Meta- analysis*

Due to anticipated heterogeneity, a random effects model was selected, with meta-analysis performed using Comprehensive Meta-Analysis software (CMA, version 3) in the stages described below.

First, we compared pain scores in AD versus HCs for each primary outcome of (1) pain threshold, (2) pain tolerance, (3) pain ratings of intensity, (4) heart rate responses to painful stimuli and (5) FACS scores. Second, we investigated potential moderators in a meta regression analysis when five or more studies were included in the pain domain, examining the influence of age, sex, cognitive symptoms scores, illness duration.

Heterogeneity was assessed with the Cochran Q and  $I^2$  statistics for each analysis [26]. Publication bias was assessed with a visual inspection of funnel plots and with the Begg-Mazumdar Kendall's tau [27] and Egger bias test [28]. If we encountered publication bias, we calculated the trim and fill adjusted analysis [29] to remove the most extreme small studies from the positive side of the funnel plot, and recalculated the effect size at each iteration, until the funnel plot was symmetric about the new effect size.

### **3.1 RESULTS**

#### *3.2 Study characteristics*

Initial searches yielded 1,122 unique hits after the removal of duplicates. After the screening process, 37 full text papers were reviewed and 24 were excluded with reasons (see figure 1). Overall, 13 articles representing 10 unique studies were included [6,17,30-40]. Three author groups [6,17,30,33,37,38] reported different pain assessment outcome measures across two separate publications within the same AD sample.

*Figure 1 here*

#### *3.3 Summary of included studies and participant details*

Across the 13 included publications there were 516 unique people, including 256 people with AD and 260 HCs. The participants with AD's mean age was 74.6( $\pm$ 5.6) years, 59% were women and the mean MMSE score was 19.2 (range 11-24). Three of the included studies confirmed a diagnosis of AD according to DSM criteria [17,30,31] whilst the remaining ten used the ICD and/ or NINCDS-ADRDA criteria. Three of the included studies included medicated participants. Among the control participants, the mean age was 73.8 ( $\pm$  5.2) years, with 63.6% females and a mean MMSE score of 29.3 (range 26.5-29.7) across 13 studies. Further details regarding the included studies and participant details are summarised in table 1.

With respect to pain modality, different pain induction methods were used as follows: Pressure (N=8), Electrical (N=4), Cold (N=2), Heat (N=3) and Ischaemic (N=1)

The mean NOS score across the studies was 5 (range 4-6) and the summary scores are presented in table 1.

*Table 1 here*

#### **3.4 Meta-analysis results**

Details of all meta-analysis results, including heterogeneity and publication bias are presented in Table 2, with key findings for each outcome measure summarised below.

### **3.5 Pain threshold**

Seven unique studies [31-34,36,39,40] including 135 people with AD and 157 HCs measured pain threshold. In the meta-analysis, there was no evidence of any difference in pain threshold between people with AD and HCs (hedges  $g$  = -0.321 to 0.371,  $p$  = 0.89) as can be seen in figure 2. There was some heterogeneity in the analysis ( $I^2$  = 52%) but no indication of publication bias (Begg = -0.38,  $p$  = 0.22, Egger = -5.16,  $p$  = 0.13).

*Figure 2 here*

### *3.6 Meta regression of moderators of pain threshold*

Meta regression analysis demonstrated that a higher percentage of females among AD participants moderated an increased pain threshold ( $\beta$  = 0.0999, 95% CI 0.015-0.1848,  $p$  = 0.021;  $R^2$  = 1.0). An increasing MMSE score suggested a decreased pain threshold between those with AD and HCs, although this was not significant ( $\beta$  = -0.0429, 95% CI -0.1098-0.014,  $p$  = 0.192,  $R^2$  = 0.42). Increasing age among AD participants also moderated a lower pain threshold score between AD and HCs, although this was not significant ( $\beta$  = -0.0311, 95% CI -0.0757-0.0135,  $p$  = 0.171,  $R^2$  = 0.71). Study quality, mean age and the percentage of females within the control group were not significant moderators of pain threshold (see table 3).

### **3.7 Pain tolerance**

Data pooled from two studies [31,34] including 41 people with AD and 53 HCs revealed no significant differences in pain tolerance ( $g$  = -0.363, 95% CI -2.035-1.309,  $p$  = 0.67).

### **3.8 Pain intensity ratings**

Data from four unique studies measured pain intensity ratings scores in 138 people with AD and 135 HCs [30,32,35,38]. There was no evidence that pain intensity ratings are different among people with AD and HCs in the meta-analysis of 273 people ( $g=0.03$ , 95% CI -0.504-0.578,  $p=0.89$ ) (figure 3).

*Figure 3*

### **3.9 Heart rate response to noxious stimuli**

Data from 3 studies [17,38,40] including 93 people with AD and 99 HCs measured heart rate response to noxious stimulation. There was a decreased heart rate response among people with AD compared to HCs, yet this did not reach statistical significance ( $g=-0.746$ , 95% CI -1.683-0.191,  $p=0.11$ ).

### **3.10 Facial Action Coding System (FACS)**

Three unique studies [30,37,39] conducted FACS assessment in 90 people with AD and 109 HCs in response to painful stimuli. The pooled data across 199 people demonstrated that people with AD have a significantly raised FACS score compared to HCs ( $g=0.442$ , 95% CI 0.034-0.850,  $p=0.03$ ). There was some heterogeneity ( $I^2=48$ ) but no evidence of publication bias (Begg=0,  $p=1$ , Egger=3.8,  $p=0.55$ ).

*Table 2 (summary of MA results)*

*Table 3 (meta-regression)*

#### 4.1 Discussion

Data from the first meta-analysis investigating response to experimentally induced pain in people with AD and HCs has produced several novel findings. Across the 13 included studies (256 people with AD and 260 HCs), we found no significant differences in pain threshold, tolerance and pain intensity ratings between people with AD and HCs. However, people with AD showed significantly raised FACS scores (suggesting amplified pain) compared to HCs when relying on observer pain ratings, suggesting a higher sensitivity for pain when evaluated with this observer rated tool. Whilst our results are novel, there were relatively few studies in several of the pain dimensions and clearly more research is required.

Taken together, our results suggest that people with AD demonstrate heightened pain sensitivity relative to controls when assessed by observer ratings (specifically the FACS), but not when assessed with methods that rely on participant ratings/response or psychophysiological response. One possible interpretation of this finding is that AD patients do experience comparatively greater pain, but that the ability to detect this may be dependent upon the measurement instrument. The observer rated FACS assessment instrument is based on the anatomical analysis of visible, pain-specific facial movements and has been shown to provide a reliable objective assessment of pain response that is not dependent upon verbal communication abilities [37]. However, the impairment in cognitive and communication abilities associated with AD may provide a threat to the reliability of assessment measures that require significant input from the patient. Self-assessment measures, which require the patient to verbally report their pain, are more likely to be negatively impacted by restricted communication and cognitive abilities that might be evident at high levels of AD [41]. Empirical data seems to support this, with several studies [17,30] finding that patients with severe AD failed to pass reliability testing for the self-reported pain rating assessment and had to be excluded from analysis. The fact that, in Beach et al [17,30], the severe AD group *did* show

evidence of increased pain on *other* measures (thereafter excluded due to reliability concerns) does seem to further support the possibility that pain differences could exist but that pain self-assessment may simply be an unsuitable measurement tool in severe AD patients to detect this. Although the impact of cognitive impairment on stimulus-dependent measures such as pain threshold and tolerance is less immediately obvious, lack of adequate explanation from the researcher of task requirements can still compromise reliability and it has been noted that many of the threshold/tolerance paradigms typically used can have quite high cognitive demands [42]. If this is true, then non-verbal assessments may potentially have greater utility for pain assessment in AD, and experimental pain research may benefit from their employment. It should be noted that no differences between AD and HCs were found in heart rate response. Although heart rate should perhaps not be automatically discounted at this preliminary stage due to the low number of studies (3), autonomic dysfunction in AD is common [43], and this is likely to complicate and potentially prohibit its use as pain assessment measure in this group. As such, measures of facial expressions such as the FACS are perhaps more promising as non-verbal measures of pain assessment for those with AD than autonomic measures.

A second, alternative explanation for the failure to find consistent differences in pain threshold, tolerance and pain intensity ratings is that, rather than these assessments failing to detect genuine group differences in pain, these specific pain dimensions are actually left intact in AD. Given the comparatively higher power of the analysis of pain threshold, which was able to examine 7 studies (N=292), it could be argued that this finding of no difference should be relatively robust. In fact, the lack of differences between AD and healthy controls in detection of pain threshold, is consistent with the fact that the cerebral areas which comprise the lateral pain system (e.g. S1), which process the sensory-discriminative aspects of pain, are thought to be subject to less neurodegeneration in AD. As pathological changes

in AD appear to be more pronounced in the areas of the brain involved in medial path pathways [6], which process the affective-motivation aspects of pain, it would perhaps be expected that tolerance would be altered in AD, as tolerance is associated with greater affective distress [48] and is more likely to be modulated by affective influences than pain threshold [44]. However, only two studies of tolerance were available for analysis greatly limiting the power of the analysis to detect genuine differences. As such, while there is stronger evidence that pain threshold is unaffected in AD, more research is needed to determine the impact on tolerance.

Although the meta-analysis of available studies precludes definitive conclusions, the observed differences between AD and HCs in FACS scores suggests potential genuine alteration of pain sensitivity in AD which is consistent with some other lines of other research. For example, nociceptive flexion reflex has been demonstrated to be decreased in AD, which suggests that pain processing is altered at the spinal column level [38]. Furthermore, a functional brain imaging study [6] found that noxious mechanical stimulation resulted in greater activation of pain-related sensory, affective and cognitive processing regions in AD patients relative to controls suggesting pain could be processed differently. However, ratings of pain unpleasantness did not differ across AD and controls, suggesting that the way in which this activity is related to the processing of noxious stimulus is complex and could even be related to attention or surprise. Given that people with AD receive fewer analgesics than healthy individuals [6] and yet no evidence was found for diminished pain in AD, the authors stated it is a clinical imperative to identify and manage pain in this group. As our results corroborate this fMRI study [6] and actually provide some evidence of *increased* pain, this adds to the calls to correctly identify and manage pain in AD. This finding also adds to calls for future

experimental research to utilise non-verbal pain assessments to better understand pain responses in people with AD.

Given the aforementioned, in clinical practice there is clearly a need to utilise clinically useful observer rated pain scales to detect pain in people with AD. Indeed, the American Geriatric and pain society recommend that for the evaluation of pain in people with dementia, facial expression should be considered for a correct evaluation of pain in these people particularly among those with marked AD [45]. Facial expressions due to pain, in fact, remain preserved even in case of important cognitive decline. Therefore, our study suggests that to evaluate pain in people with AD, observer rated pain assessment scales should be used in this population at higher risk of painful events due to higher presence of co-morbidities. However, it is important to note that, the research examining the ability of the FACS to differentiate markers of pain from other emotional states is limited. In addition, behavioural changes occur in AD as the disease progresses, and it has even been suggested that facial responses to pain are different in AD simply because the cognitive ability to regulate the behavioural expression of pain becomes impaired [37] [49]. These progressive changes in behavioural expression in AD could potentially confound the usefulness of these assessments. At the same time, measures such as the FACS have shown good ability to differentiate pain from baseline, non-painful states, and higher FACS scores have been linked to higher levels of noxious stimulation [30,37,39]. Overall, the utility of facial expression assessments as pain assessments in AD and the likelihood of their adoption in any kind of clinical setting is likely to depend partly on the ability of these type of measures to empirically demonstrate both specificity in differentiating pain from other emotions and from progressive behavioural changes that occur in AD.

Among the experimental findings requiring self-report from AD participants, we found no evidence of a difference in pain threshold (the point at which pain is first perceived) between

AD and controls. Among the moderators of pain threshold was that a higher percentage of females among AD participants moderated the difference in pain threshold between those with AD and HCs. This seems an important point since some previous research has demonstrated that older women are more sensitive to pain than older men [46] and the differences in the number of females could partly explain our findings. Moreover, meta regression analysis also highlighted that higher MMSE scores in AD participants (indicating less cognitive impairment) is associated with a reduced difference in pain threshold in AD versus HCs suggesting that cognitive function is an important determinant in showing pain manifestations. Therefore, although affected by AD, people with sufficient cognitive function are able to report if they are or not affected by pain, similar to healthy controls.

The current findings should be considered within its limitations. First, the relatively small number of studies imposed limits on the range of pain parameters that could be examined and the analyses that could be conducted. For example, it was not possible to conduct separate analyses at different stages of the disease, and in particular for severe and less severe levels of cognitive impairment. Whilst our meta regression found that differences between AD v HCs in pain threshold were not moderated by cognitive impairment as assessed by MMSE scores, this non-significant result should be viewed cautiously given the relatively few studies involved. Given that cognitive impairment in those with AD was within the mild-moderate range, it remains unclear if the results extend to people with AD who have severe cognitive impairment. Future research should include those with more marked cognitive decline, whilst carefully navigating the ethical dilemmas of such research [47]. Second, there was a distinct paucity of information regarding neuropsychiatric symptomology and mental health outcomes (e.g. depression) and other scales for assessing cognitive status (e.g. clinical dementia rating) among the included studies, precluding meta-analysis or meta regression, and such factors could potentially affect pain sensitivity. Therefore, future research should

investigate the impact of these factors on pain sensitivity in those with AD. Thirdly, variation in ratings of research quality was observed, with NOS scores of 4 to 6 (mean=5) suggesting that overall study quality ranged from low to moderate. This was largely attributed to the small number of participants in each study and potential lack of representativeness of the wider AD population. Although our meta-regression with NOS scores as a moderator found no evidence that study quality appeared to influence differences between ADs and HCs, sample sizes should ideally be larger to provide optimal power for detection of any such moderation. Furthermore, it is possible that studies designated as low quality (especially the 2 from 13 studies where NOS ratings=4) could provide sub-optimal data that might influence the integrity of the findings. In light of this, future studies of higher quality are needed to substantiate the pattern of results from studies conducted so far and examined in this meta-analysis. Nevertheless, allowing for these caveats, our results provide a solid foundation for further investigation and add to the growing body of literature and suggest that it may be important to include measures other than self-report assessments when assessing pain in those with AD. In particular, our findings add to the calls for the management of pain and identification with observer rated scales such as the FACS.

In conclusion, our meta-analysis suggests that people with AD have similar self-rated pain threshold and tolerance compared to controls. This result could be accounted for by challenges in communication relating to cognition. Our data also found significantly higher observer-rated FACS scores than healthy controls. More research is needed about how to evaluate pain reliable and valid in people with AD, also in experimental settings.

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### **Conflict of Interest**

None from any author.

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### **Data Access, Responsibility, and Analysis**

BS had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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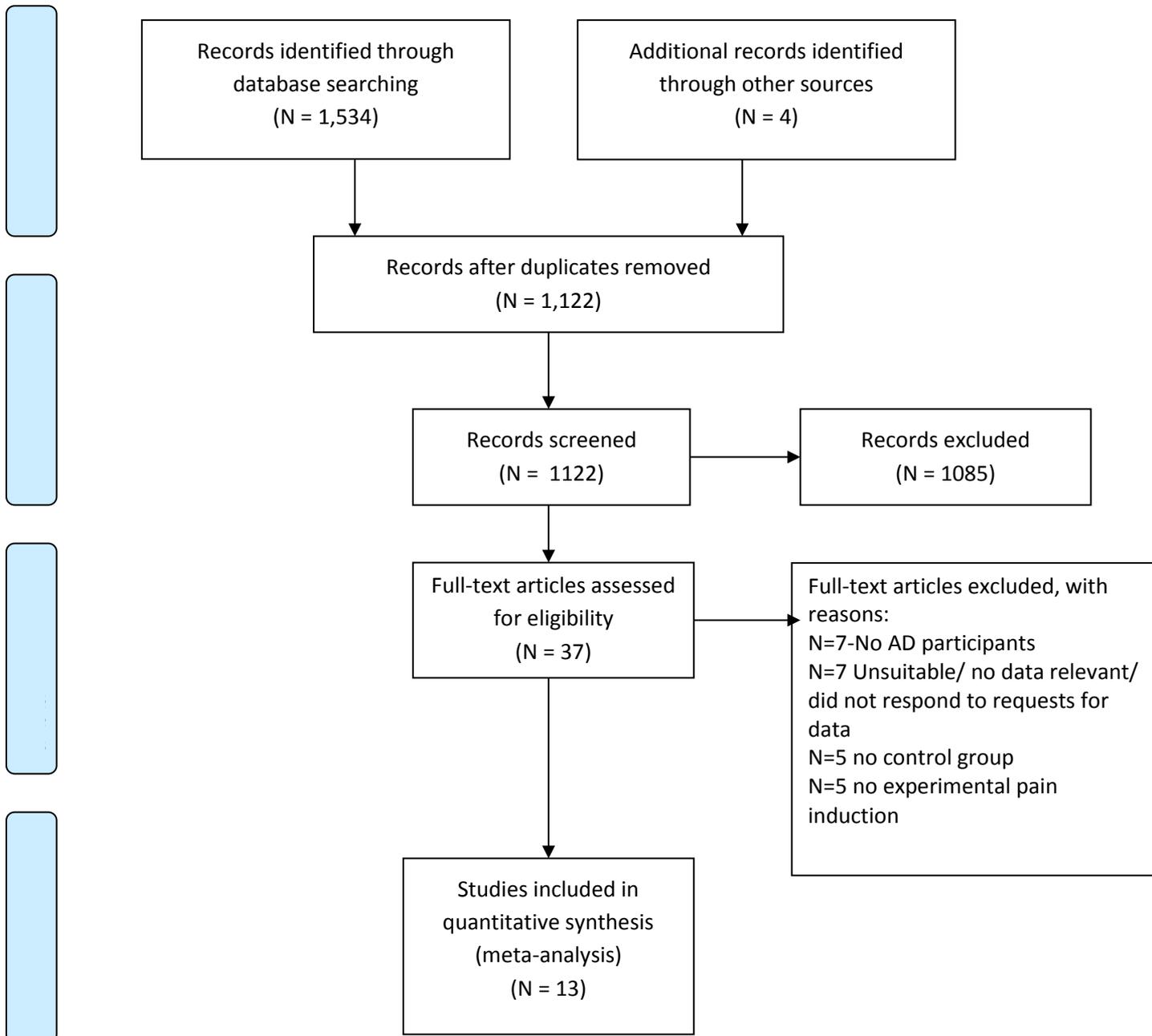
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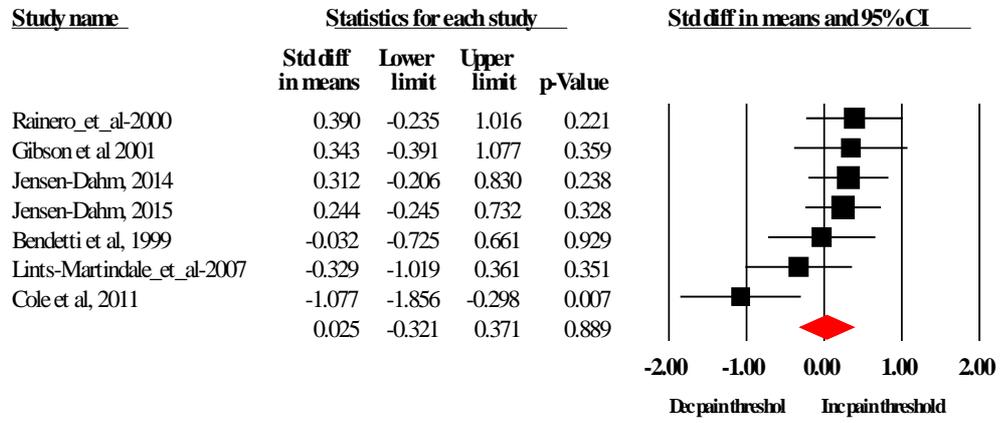
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**Figure 1. Prisma flow diagram**



**Figure 2 – Meta analysis of pain threshold in AD and controls**



**Figure 3 Differences in pain intensity ratings in AD and controls**

