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Does the presence of chronic pain affect scores on cognitive screening tests/brief cognitive measures for dementia? A systematic review and meta-analysis

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ABSTRACT

Objective: Cognitive screening tests can identify potential dementia by indicating a concerning level of cognitive impairment. The older populations for whom this is most relevant are more likely to experience chronic pain, which also impairs cognitive function, but pain's impact on cognitive screening tests specifically remains unknown.

Method: We conducted a systematic review and meta-analysis (SR/MA) following PRISMA guidelines evaluating cognitive screening scores in studies involving participants with chronic pain compared with a pain-free control group. Our question was whether the presence of chronic pain (self-reported or based on diagnosis) was associated with poorer performance on these screens, and to identify the heterogeneity across groups and screens. **Results:** The 51 studies identified yielded 62 effect size estimates. The pooled g was 0.76 (95% confidence interval 0.57 to 0.95). Heterogeneity was high for the full model ($= 93.16\%$) with some reductions in sub-analyses. Around half of the studies were identified as being at a low risk of bias. There was no evidence of publication bias. **Conclusions:** As a whole, this analysis suggests medium to large effect sizes on cognitive screen performance when people are living with chronic pain. We suggest that clinicians should consider the effect of chronic pain when cognitive screens are employed to investigate dementia. Further research could clarify the effect pain has on different screen sub-domains to aid their effective use with these populations.

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KEYWORDS


Dementia; pain; cognition; cognitive screen; meta-analysis

Introduction

Rationale

Cognitive screening tools are measures designed to detect cognitive impairment through brief means, typically within 20 min (Cullen et al., 2007). These target either one highly predictive ability or core domains (e.g. language, memory, attention) using

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a minimal set of items. While cognitive screening is used for many conditions such as brain tumors, psychiatric disorders, and traumatic brain injuries (Roebuck-Spencer et al., 2017), a common rationale for their development is to screen for dementia.

In some instances, low cognitive screen scores that corroborate deficits reported at clinical interview may help clinicians reach a diagnosis. Screening scores also aid in determining the need for more in-depth assessment conducted by clinical psychologists and neuropsychologists, assessment which is typically time-intensive and cognitively demanding. Cognitive screens should thus be sufficiently sensitive—correctly identifying when follow-up is warranted, to maximise early diagnosis - and specific—avoiding putting people onto an unnecessary investigative pathway (Cullen et al., 2007).

Key to diagnostic accuracy is understanding how other factors may influence screen performance besides the presence of dementia. For instance, while the screening measure Addenbrooke's Cognitive Examination-III (ACE-III) appears reasonably robust to levels of premorbid intelligence of the test-taker (Stott et al., 2017), other frequently used screens such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) show an influence of intelligence (Alves et al., 2013), leading those researchers to recommend premorbid IQ scores be considered alongside the test results. Environmental factors have also been noted as influential, with Dupuis et al. (2016) reporting a three-point decrement on the MoCA when completing the measure under noisy conditions. Performance concerns also apply to populations with co-morbid conditions that may affect cognition, such as chronic pain.

When someone experiences chronic pain they are more likely to report problems with memory, attention and thinking (McCracken & Iverson, 2001). Pain is known to affect performance on neuropsychological tests and batteries, on domains including attention, speed of information processing and executive function, as described by Moriarty et al. (2011).

These authors note that potential mechanisms driving this impairment include resource depletion and disrupted attention due to pain symptoms; for chronic pain, further possibilities are concomitant analgesic use and longer-term neurological changes due to the pain condition or sustained experience of pain. As chronic pain is more prevalent with aging (Schofield, 2007), clinical psychologists and neuropsychologists who work in dementia services are likely to be presented with cognitive screening scores for people living with chronic pain, and to make judgments on how to interpret these. It is, therefore, important to understand whether the experience impacts cognition sufficiently to result in alterations of cognitive screen performance.

Further reviews provide more detail on the impact of chronic pain on aspects of cognition. Meta-analyses of performance in working memory are described by Berryman et al. (2013) and in executive function by Berryman et al. (2014). For rheumatoid arthritis specifically, Pankowski et al. (2022) present meta-analyses showing cognitive impairment across several domains, and Meade et al. (2018) note impairments particularly in memory, attention and verbal function. A review of fibromyalgia by Schmidt-Wilcke et al. (2010) summarizes problems in free recall, working memory and a mixed pattern of results around attention.

In the main, these studies do not focus on cognitive screening tools. The primary exception is a review on rheumatoid arthritis by Pankowski et al. (2022) which

reports estimated effect sizes for two such measures, the MMSE (based on eight comparisons) and the MoCA (based on three comparisons), finding respective standardized mean differences of .66(95% CI 0.42–0.90) and 1.27 (95% CI 0.68–1.87). This suggests pain conditions may be associated with poorer performance on cognitive screens used to investigate dementia. However, this may not generalize to other conditions, especially as other mechanisms for cognitive impairment are suspected for rheumatoid arthritis (such as impact on intracranial circulation, see e.g. Oláh et al., 2017).

Objectives

The aim of this study was to conduct a systematic review/meta-analysis to assess the impact of chronic pain upon cognitive screen performance.

Materials and methods

The study followed the PRISMA guidelines for reporting SRs and MAs (Moher et al., 2009), with a checklist of the steps completed found in [Appendix 1](#). The protocol of the study was registered with the International Prospective Register of Systematic Reviews ([INB registration number available once masked review stage completed] and published elsewhere (anonymized view https://osf.io/jsqxn/?view_only=237cdaa33511422890730eb1de49d44d); this includes an analysis plan released prior to the work being conducted. The protocol was updated 14 May 2022 to clarify that comparisons must involve pain-free controls.

Eligibility criteria

The review focused on primary research that satisfied a set of PECO criteria—(P)opulation, (E)xposure, (C)omparator, (O)utcomes—defined as follows: in (P) participants of any sex aged 18 or over investigate (E) the effect of having chronic pain versus (C) controls without chronic pain on (O) cognitive screening tool performance. Studies could include cross-sectional as well as experimental designs unless the available screening data were confounded by an introduced treatment. Studies were excluded if they involved samples with a diagnosed cognitive impairment due to a disease originating in the brain, such as stroke, traumatic brain injury or dementia.

Definitions of cognitive screening tools are varied and are the subject of a number of previous systematic reviews (e.g. Ashford, 2008; Cullen et al., 2007). This SR utilized a practitioner definition provided by the Alzheimer's Society (2013), which reports nine screens agreed by UK clinicians to be appropriate for common clinical practice, being: Addenbrooke's Cognitive Examination-III (ACE-III), Abbreviated Mental Test (AMT), Mini-Cog, Montreal Cognitive Assessment (MoCA), Mini Mental State Examination (MMSE), 6-item Cognitive Impairment Test (6CIT), Hopkins Verbal Learning Test (HVL), Test for the Early Detection of Dementia (TE4D-Cog), and Test Your Memory test (TYM). Studies using different editions and language variants of these screens were eligible.

Information sources

PROSPERO and Epistimonikos were searched for similar ongoing or recently completed SRs on 5 April 2021. Searches of bibliographic databases were conducted on 17 September 2021 via: Ovid for Embase (1947–present), and EBSCOhost for Medline (1946–present) and PsycINFO; a mapping of articles from preliminary searches showed these databases achieved saturation. OpenGrey (System for Information on Grey Literature in Europe) was separately searched for identification of relevant non peer-reviewed research in January 2021.

Search strategy

Database searches were designed using the PECO model described above. Exposure was operationalized in title and abstract by identification of key pain-related conditions (fibromyalgia, arthritic, and rheumatic conditions), headache/migraine, or the terms chronic and pain with no more than four words separating them, or report of a standardized pain measure (e.g. McGill Pain Questionnaire); where available medical headers for pain were used. Population was defined by use of Medical Headers. Outcome was operationalized by full names and abbreviations of the nine cognitive measures in title and abstract and where available tests and measures fields. No comparator information was used to define the search parameters. Searches were initially piloted in PsychINFO before adaptation for use in the other databases. Full search strategies for each database can be found in [Appendix 2](#).

Hand-searches were made prior to search to identify relevant studies that met criteria, using keywords and reviews identified by searching Epistimonikos and PROSPERO. Further studies were identified through a review article discovered subsequent to search completion. Due to the number of final studies obtained back- or forward-citation searches were deemed unnecessary.

Selection process

After acquiring search results and removal of duplicates, two initial co-review stages were completed by reviewers 1 (AF) and 2 (JM). Stage one began by calibrating the eligibility checklist on 10 title-abstracts and agreeing refinements. After this both reviewers independently screened 120 titles and abstracts against inclusion criteria, discussing discrepancies in judgment until reaching consensus on all cases (consulting with a third author where necessary). AF then completed sifting of titles and abstracts. In stage 2, the full-texts of two retained studies were reviewed by both reviewers to calibrate eligibility. These reviewers then independently screened 20 further full texts, addressing discrepancies as per stage 1. AF completed the full text review on all remaining results. Authors were contacted when full articles were unavailable ($n=1$). Studies had to meet one of two criteria for chronic pain: experience of pain at one or more body locations for at least 3 months at the time of study involvement, or diagnosis with a condition known to involve chronic pain such as fibromyalgia, arthritis, or any condition found on the lists of chronic pain conditions provided by the International Association for the Study of Pain (IASP) (Merskey & Bogduk, 1994, lists

1 A, 1 F, 1 H). Full guidelines for reviewers for both title-abstract and full-text screening can be found in [Appendix 3](#).

Data extraction and items

Data were extracted by AF, with JM performing a check to ensure accurate extraction on five consecutive papers, which was achieved after eight papers. Authors were contacted when data was partially incomplete (e.g., means but no standard deviations), appeared to contain errors, or potentially duplicated data from another study. Relevant data included type of pain condition, participant details, measures of pain and mood and scores on the cognitive screening test (mean and standard deviation, or median and inter-quartile range), as well as whether the test was key or incidental to the study (e.g. a baseline measure). Where data were provide on multiple outcomes (cognitive screens) all outcomes were extracted. A data dictionary can be found at the OSF folder.

Quality assessment tool

Study quality was assessed using the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (Moola et al., 2017). The checklist includes items that required some adaptation for relevance in this review, which was supplied to both reviewers as supplementary guidance reproduced in [Appendix 4](#). Briefly, the items concerned: 1) criteria for sample inclusion; 2) describing subjects and demographics; 3) measurement of pain with a validated tool; 4) not used as deemed redundant for this SR; 5) reporting confounding factors of age, education, mood and medication usage; 6) matching or controlling for age and education¹; 7) reporting information about screen administration; 8) appropriate screen data available without floor effects introduced by a cognitive screen cutoff. No overall risk of bias score is produced using this tool. Reviewers AF and JM independently reviewed quality for five studies before meeting to address discrepancies. This meeting identified overlap on how the criteria were being applied and led to clarification within the supplementary guidance, after which further quality assessment was completed by AF.

Statistical analyses—effect measures and synthesis

Cognitive screen means and standard deviations were used to compute standardized mean differences (SMD) in the form of Hedges' *g* using the approach described by Hedges and Olkin (1985). Scores reflect the size of effect due to pain status with larger positive scores reflecting greater impairment in the chronic pain group. Where data were presented as median and inter-quartile range, this was converted into estimated mean and standard deviation with the *estmeansd* R package using the Box-Cox method described in McGrath et al. (2020).

Analyses were conducted using the *metafor* package (Viechtbauer, 2010) with a random-effects model using restricted maximum-likelihood (REML) estimation to measure between-study variance and producing a Wald-type confidence interval. Individual and aggregated effect sizes were visualized using forest plots. A multi-level meta-analytic approach was taken as for a number of studies more than one

comparison of cognitive screen scores fit review criteria (due either to multiple chronic pain groups compared to one control group or two cognitive screens administered across participants). In most instances, this led to generating multiple standardized mean differences per study.² This produces interdependency between outcomes best addressed by a multi-level approach to pooling data. This involved a correlated and hierarchical effects model which drew on a covariance matrix estimating these interdependencies, incorporating information about the relationships between cognitive screen scores. We also explored whether results differed when employing robust variance estimation methods to further account for non-independence. Details are provided in [Appendix 5](#). Three types of subgroup analysis were considered. One approach was to use data from a single cognitive screening measure; a second those involving data from a single pain condition. A third approach was to stratify the groups by age. These analyses were attempted for situations where five or more comparisons were available. Analysis code is available at [anonymous link] https://osf.io/jsqxn/?view_only=237cdaa33511422890730eb1de49d44d.

Reporting bias assessment

A funnel plot was produced to investigate whether results may be missing in a non-random fashion due to reporting bias. In many studies, our measure of interest (cognitive screen) was incidental to the wider motive for the research (e.g., merely to report sample characteristics). The funnel plot excluded these studies to consider only those where the findings hinged on the cognitive screening data, to identify whether there has been a systematic under-reporting of non-significant findings.

Results

Study selection

A total of 3505 records were identified, 485 of which were initially identified as duplicates. Following two sifting stages (an additional step was made when accessing full-texts to dispose of a large number of conference abstracts), 140 were examined in full text. This led to 45 studies that appeared to meet inclusion criteria, but we excluded one study (Han et al., 2013) that did explicitly report a chronic pain group but using a minimum duration of 1 month of pain (rather than three), with no diagnostic information or mean duration reported to verify that this would constitute chronic pain by our criteria. Seven further articles were identified by hand-searching prior to and following the search; these involved studies discovered in review papers (e.g., of arthritis) that either did not refer to pain in key words/title/abstract or did not make explicit that it contained cognitive screening data. This leads to 51 studies in total. [Figure 1](#) depicts this as a flow diagram.

Study characteristics

The search process led to the extraction of 63 effect size estimates from 51 studies. Data from 7,054 people experiencing chronic pain and 5917 pain-free controls were extracted.

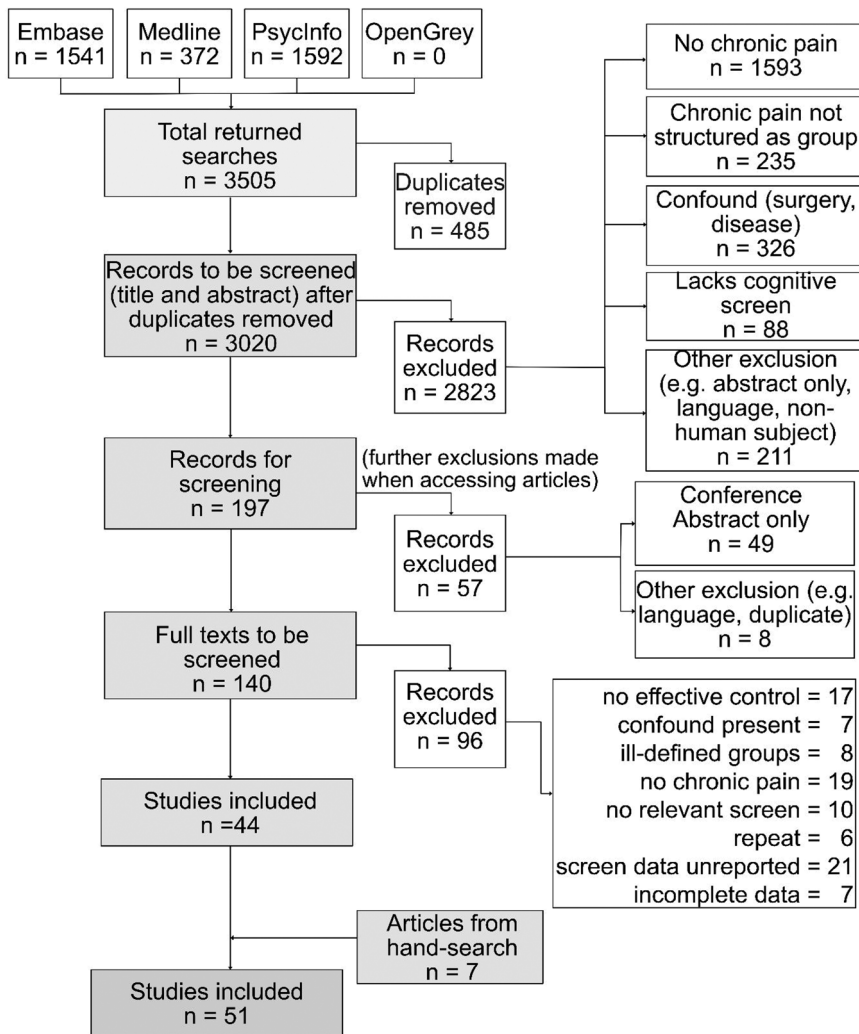


Figure 1. PRISMA flow diagram.

There were 37 comparisons involving the MMSE, 19 for the MoCA, 3 for the TYM, 2 for the ACE, and 1 for the HVLT. Information on reliability for these instruments can be found in [Appendix 5](#). In 36 comparisons, the screen was part of the study focus and 26 where the screen was used merely to inform the description of samples. [Table 1](#) presents summary information on these studies. [Appendix 5](#) includes a table reporting those studies for which ratings on a pain instrument are reported (group means and standard deviations).

Risk of bias in studies

Only three comparisons (from two studies) met every JBI criterion. The majority of comparisons ($k=48$) did adequately describe sample details and inclusion criteria as per criterion 1 and 2. However a minority of comparisons met criteria 3 ($k=10/62$) or 5 ($k=NA$) due, respectively, to lack of pain measurement in both control and pain

Table 1. Characteristics of studies.

Authors	Country	Pain group	Patient group <i>n</i>	Education	Patient age - Mean (SD)	Screen
Al-Malki et al. (2020)	Egypt	Chronic tension-type headache	100	no sig diff	35.31 (6.95)	MoCA
Baptista et al. (2017)	Brazil	Rheumatoid arthritis	20	no sig diff	56.9 (9.2)	MMSE
Barceló-Martinez et al. (2018)	Colombia	Fibromyalgia	30	no sig diff	52 (8.9)	MMSE
Rattay et al. (2020)	Germany	Hereditary spastic paraplegia	26	higher for controls	50.6 (9.5)	MoCA
Borg et al. (2015)	USA	Fibromyalgia	18	higher for controls	50.39 (9.87)	MoCA
Buckalew et al. (2008)	USA	Older adults self-reporting chronic lower back pain	8	no sig diff	74.5 (4.2)*	MMSE
Can et al. (2012)	Turkey	Fibromyalgia	50	no sig diff	35.9 (8.2)	MMSE
Canfora et al. (2021)	Italy	Burning Mouth Syndrome	40	no sig diff	65.63 (8.59)	MMSE
Cardoso et al. (2021)	USA	Community dwelling older adults reporting chronic pain	39	no sig diff	71.1 (6.1)	MoCA
Z. Chen et al. (2016)	China	Chronic migraine	16	higher for controls	42.4 (8.7)	MoCA
Z. Chen et al. (2016)	China	Chronic migraine	16	higher for controls	42.4 (8.7)	MMSE
Coelho Rebelo Maia (2012)	Portugal	Rheumatoid arthritis	45	no sig diff	41.07 (9.68)	MMSE
Corti et al. (2021)	Australia	Chronic lower back pain	31	no sig diff	56.9 (14.62)	HVLT
Demirci and Savas (2002)	Turkey	Chronic lower back pain	23	not reported	47.6 (12)	MMSE
Di Carlo et al. (2021)	Italy	Psioratic arthritis	96	no sig diff	52.7 (11.7)	MoCA
El-Shafey et al. (2012)	Egypt	SLE	30	no sig diff	34.56 (6.01)	MoCA
Fayed et al. (2012)	Spain	Fibromyalgia	10	not reported	38.94 (5.56)	MMSE
Fayed et al. (2012)	Spain	Somatisation disorder	10	not reported	43.92 (9.96)	MMSE
Fayed et al. (2017)	Spain	Fibromyalgia	12	unclear	41.7 (7.3)	MMSE
Feng et al. (2020)	China	Osteonecrosis of the femoral head	10	not reported	54.3 (19)	MMSE
Foss et al. (2016)	Brazil	Outpatients with self-reported non-oncologic chronic pain	45	no sig diff	46.9 (11.9)	MoCA
Garcia et al. (2021)	Brazil	Psioratic arthritis	37	no sig diff	57.37 (13.48)	MoCA
Güzel et al. (2018)	Turkey	Rheumatoid arthritis (active)	45	no sig diff	55.73 (10.36)	MMSE
Gwinnutt et al. (2021)	UK	Rheumatoid arthritis	38	higher for controls	69.1 (8)	ACE-III
Hamed et al. (2012)	Egypt	Rheumatoid arthritis	55	no sig diff	41.9 (6.8)	MMSE
Karp et al. (2008)	USA	Older adults with self-reported pain	476	no sig diff	73.4 (5.9)	MMSE
E. J. Kim and Buschmann (2006)	Korea	Older adults with self-reported pain	85	higher for patients	72.85 (5.42)†	MMSE
Kotb et al. (2019)	Egypt	Rheumatoid arthritis	30	not reported	44.97 (9.58)	MoCA
Li et al. (2018)	China	Mixed chronic pain, self-reported	3,250	not reported	higher for patients	MMSE
Liao et al. (2018)	China	Knee osteoarthritis	30	not reported	56.5 (6.8)	MoCA
Liao et al. (2018)	China	Knee osteoarthritis	30	not reported	56.5 (6.8)	MMSE
Z. Chen et al. (2017)	China	Medication overuse headache	44	not reported	42.3 (9.62)	MoCA
Maneeton et al. (2010)	Thailand	SLE - no CNS involvement	19	no sig diff	31.3 (8.2)	MMSE
Mednieks et al. (2021)	United Arab Emirates	Rheumatoid arthritis	20	no sig diff	55.44 (12.53)	MoCA
Ojeda et al. (2016)	Spain	Neuropathic chronic non-malignant pain	104	no sig diff	45.6 (8.7)*	MMSE

(Continued)

Table 1. Continued.

Authors	Country	Pain group	Patient group <i>n</i>	Education	Patient age - Mean (SD)	Screen
Ojeda et al. (2016)	Spain	MSK chronic non-malignant pain	99	no sig diff	47.6 (9.4)*	MMSE
Ojeda et al. (2016)	Spain	Fibromyalgia	51	no sig diff	50.8 (6.7)*	MMSE
Ojeda et al. (2016)	Spain	Neuropathic chronic non-malignant pain	104	no sig diff	45.6 (8.7)*	TYM
Ojeda et al. (2016)	Spain	MSK chronic non-malignant pain	99	no sig diff	47.6 (9.4)*	TYM
Ojeda et al. (2016)	Spain	Fibromyalgia	51	no sig diff	50.8 (6.7)*	TYM
Oláh et al. (2020)	Hungary	Rheumatoid Arthritis	60	no sig diff	60.7 (9.5)	MoCA
Oosterman et al. (2011)	Netherlands	Mixed chronic pain diagnoses	34	no sig diff (IQ)	51.5 (20.4)	MMSE
Petersen et al. (2015)	Brazil	Rheumatoid arthritis	30	no sig diff	50.6 (13.45)	MMSE
Petersen et al. (2018)	Brazil	Rheumatoid arthritis (active)	67	no sig diff	55.9 (11.9)	MMSE
Petersen et al. (2018)	Brazil	Rheumatoid arthritis (controlled)	35	no sig diff	57.2 (7.3)	MMSE
Petra et al. (2020)	Romania	Rheumatoid arthritis	29	no sig diff	50.6 (12.3)	MMSE
Qu et al. (2018)	China	Chronic tension-type headache	51	no sig diff	37.6 (12.6)	MoCA
Ruscheweyh et al. (2018)	Germany	Nonspecific chronic spinal pain	30	unclear	51.7 (13.5)	MMSE
Segura-Jiménez et al. (2015)	Spain	Fibromyalgia	459	higher for controls	52.2 (7.1)	MMSE
Seo et al. (2017)	Korea	Phantom limb pain	10	not reported	43.8 (3.4)	MMSE
Shehata et al. (2010)	Egypt	SLE (non-neuropsychiatric)	12	no sig diff	24.9 (7.6)	MMSE
Terassi et al. (2021)	Brazil	Older adults with chronic pain	88	no sig diff	70.55 (6.63)	ACE-Revised
Tiwari et al. (2021)	India	Fibromyalgia	30	not reported	40.6 (8.7)*	MMSE
Torkamani et al. (2015)	UK	Chronic cluster headache	11	no sig diff	49.18 (11.02)	MMSE
Veldhuijzen et al. (2012)	Netherlands	Fibromyalgia	35	higher for controls	30.4 (8.6)	MMSE
Vitturi et al. (2019)	Brazil	Rheumatoid arthritis	210	no sig diff	57.3 (12.3)	MoCA
Vitturi et al. (2019)	Brazil	Rheumatoid arthritis	210	no sig diff	57.3 (12.3)	MMSE
R. Wang et al. (2014)	China	Cluster headache	17	not reported	35.4 (NA)	MoCA
R. Wang et al. (2014)	China	Cluster headache	17	not reported	35.4 (NA)	MMSE
Y. Wang et al. (2014)	China	Idiopathic trigeminal neuralgia	36	no sig diff	56.4 (8.49)	MoCA
Weiner et al. (2006)	USA	Chronic lower back pain	163	no sig diff	73.6 (5.2)	MMSE
Xiang et al. (2021)	China	Medication overuse headache	88	no sig diff	50.01 (14.49)	MoCA

Note. MSK: Musculo-skeletal condition; SLE: Systemic Lupus Erythematosus; ACE: Addenbrooke's Cognitive Examination (R=Revised, III = 3rd edition); HVLT: Hopkins Verbal Learning Test; MMSE=Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; TYM: Test Your Memory test.

† denotes patients significantly older, * controls significantly older. NB Li et al. reported significant age differences but age data did not allow extraction of a mean and standard deviation.

groups and non-reporting of mood, education, age or medication information. Half of comparisons ($k=30$) failed to control for education and age (criterion 6) and around half ($k=30$) failed to provide information about administration of the cognitive screen (criterion 7). Finally, 16 studies showed bias on criterion 8, involving a floor on screening scores due to exclusion of low-scoring participants (Figure 2).³

As the appraisal tool does not provide guidance as to how to categorize studies as high or low risk of bias, we considered the implications of failing to meet each criterion and determined that for this SR, studies with low risk of bias were those meeting these key criteria:

Author	1	2	3	5	6	7	8
Al-Malki et al. (2020)*	●	●	●	●	●	●	●
Baptista et al. (2017)*	●	●	●	●	●	●	●
Barceló-Martínez et al. (2018)*	●	?	●	●	●	●	●
Borg et al. (2015)	●	●	●	●	●	?	●
Buckalew et al. (2008)	●	●	●	●	●	?	●
Can et al. (2012)*	●	●	●	●	●	●	●
Canfora et al. (2021)*	●	●	●	●	●	●	●
Cardoso et al. (2021)	●	●	●	●	●	●	●
Chen et al. (2016)	●	●	●	●	●	●	●
Coelho Rebelo Maia (2012)	●	?	●	●	●	●	●
Corti et al. (2021)	●	●	●	●	●	?	●
Demirci & Savas (2002)	?	●	●	●	●	●	●
Di Carlo et al. (2021)*	●	●	●	●	●	●	●
El-Shafey et al. (2012)	●	●	●	●	●	●	●
Fayed et al. (2012)	●	●	●	●	●	●	●
Fayed et al. (2017)	●	?	●	●	●	●	●
Feng et al. (2020)	?	?	?	●	●	●	●
Foss et al. (2016)*	●	●	●	●	●	●	●
Garcia et al. (2021)*	?	●	●	●	●	●	●
Gwinnutt et al. (2021)	●	●	●	●	●	●	●
Güzelet al. (2018)*	●	●	●	●	●	●	●
Hamed et al. (2012)*	●	?	●	●	●	●	●
Karp et al. (2008)*	●	●	?	●	●	●	●
Kim & Buschmann (2006)	●	●	●	●	●	●	?
Kotb et al. (2019)	●	●	●	●	●	●	●
Li et al. (2018)	●	●	●	●	●	●	●
Liao et al. (2018)	●	●	●	●	●	●	●
Ma et al. (2017)	●	●	●	●	●	●	●
Maneeton et al. (2010)*	●	●	●	●	●	●	●
Mednieks et al. (2021)	?	●	●	●	●	?	●
Ojeda et al. (2016)	●	●	●	●	●	●	●
Oláh et al. (2020)*	●	●	?	●	●	●	●
Oosterman et al. (2011)	?	●	●	●	●	●	●
Petersen et al. (2015)	?	●	●	●	●	●	●
Peterson et al. (2018)*	●	●	●	●	●	●	●
Petra et al. (2020)*	●	●	●	●	●	●	●
Qu et al. (2018)*	●	●	?	●	●	●	●
R. Wang et al. (2014)	●	●	●	●	●	●	●
Rattay et al. (2020)	?	●	?	●	●	●	●
Ruscheweyh et al. (2018)	?	●	●	●	●	●	●
Segura-Jiménez et al. (2015)	●	●	●	●	●	●	?
Seo et al. (2017)	●	●	●	●	●	●	●
Shehata et al. (2010)*	?	●	●	●	●	●	●
Tiwari et al. (2021)	●	●	●	●	●	●	●
Torkamani et al. (2015)*	●	●	?	●	●	●	●
Veldhuijzen et al. (2012)	●	●	●	●	●	?	●
Vitturi et al. (2019)*	●	●	●	●	●	●	●
Weiner et al. (2006)	●	●	●	●	●	●	●
Xiang et al. (2021)*	●	●	●	●	●	●	●
Y. Wang et al. (2014)*	?	●	●	●	●	●	●

Figure 2. Risk of bias plot. Asterisks denote those determined to have low risk of bias. Column numbers are JBI items. Criterion 4 not utilized due to redundancy with other items in this context.

adequate exclusion criteria (J1)

controlled or matched for age and education (J6)

did not employ a cut-off that prevented detection of poor performance (J8)

This resulted in 24 comparisons with a low risk of bias.

As criterion 6 does not evaluate controlling for mood, this was evaluated separately: mood disturbance was significantly higher for the pain group in 41 of the comparisons, with 13 not reporting mood and only 8 reporting similar levels of mood.

Results of syntheses

For the meta-analytic calculations, we first employed the random effects multi-level meta-analytic model using the full dataset. The pooled SMD estimate (with a positive effect denoting degree of impairment in pain groups) was 0.76 with the 95% confidence interval ranging from 0.57 to 0.95. This describes the range within which we expect the average effect size to fall. A comparison of dataset heterogeneity against within-comparison variances suggests that the comparisons reflect different effects (Cochran's $Q=481.90$, $p<.0001$). The estimated variance components were $\tau_{Level3}^2 = 0.25$ and $\tau_{Level2}^2 = 0.15$, meaning that between-study variation accounts for 58.63% of the total variation, whereas 34.53% is due to variability between multiple comparisons within a single study. [Figure 3](#) depicts the SMDs for each comparison.

Subgroup analysis

A simple random effects model produced a higher pooled SMD estimate, suggesting that effect non-independence was evident, thus justifying the multi-level approach where clusters existed. A sensitivity analysis using robust variance estimators produced almost identical outputs to the standard multi-level method. A further sensitivity analysis focused on comparisons with a low risk of bias as well as the remainder (high risk of bias). Sub-analyses were then conducted with i) MMSE screen only ii) MoCA screen only iii–vi) individual pain conditions, employing the multi-level approach when the data-set contained clusters and vii) including only comparisons where groups had similar levels of mood. Age of participants varied within and across studies with a high degree of overlap, which prevents operationalizing age as a moderator variable. Instead, we categorized studies into “young” and “old” buckets depending on whether the majority of participants in the patient group would have fallen above or below the weighted mean age of the full dataset (55): where sample mean plus sample standard deviation was below 55, assigned as young, where sample mean minus sample standard deviation was above 55, assigned as old). We also designated an “oldest” group where the majority of participants were over 65, using comparable criteria. These data are reported in [Table 2](#) and summarized here, reporting the correlated hierarchical effects model information when available).

Limiting analysis to low risk of bias studies found a slightly smaller estimate of effect size with narrower 95% confidence interval (0.667, CI 0.46–0.874), whereas the group of high risk of bias studies had both a larger effect size and wider confidence interval (0.876, CI 0.534–1.218). Within the pain subgroups, the smallest effect size was for the musculoskeletal conditions group (0.481, CI 0.175–0.788), intermediate for arthritis (0.751, CI 0.505–0.997) and largest for samples experiencing fibromyalgia (1.069, CI 0.39–1.747) and headache (1.102, CI 0.075–2.128), although these latter groups also showed much wider confidence intervals.

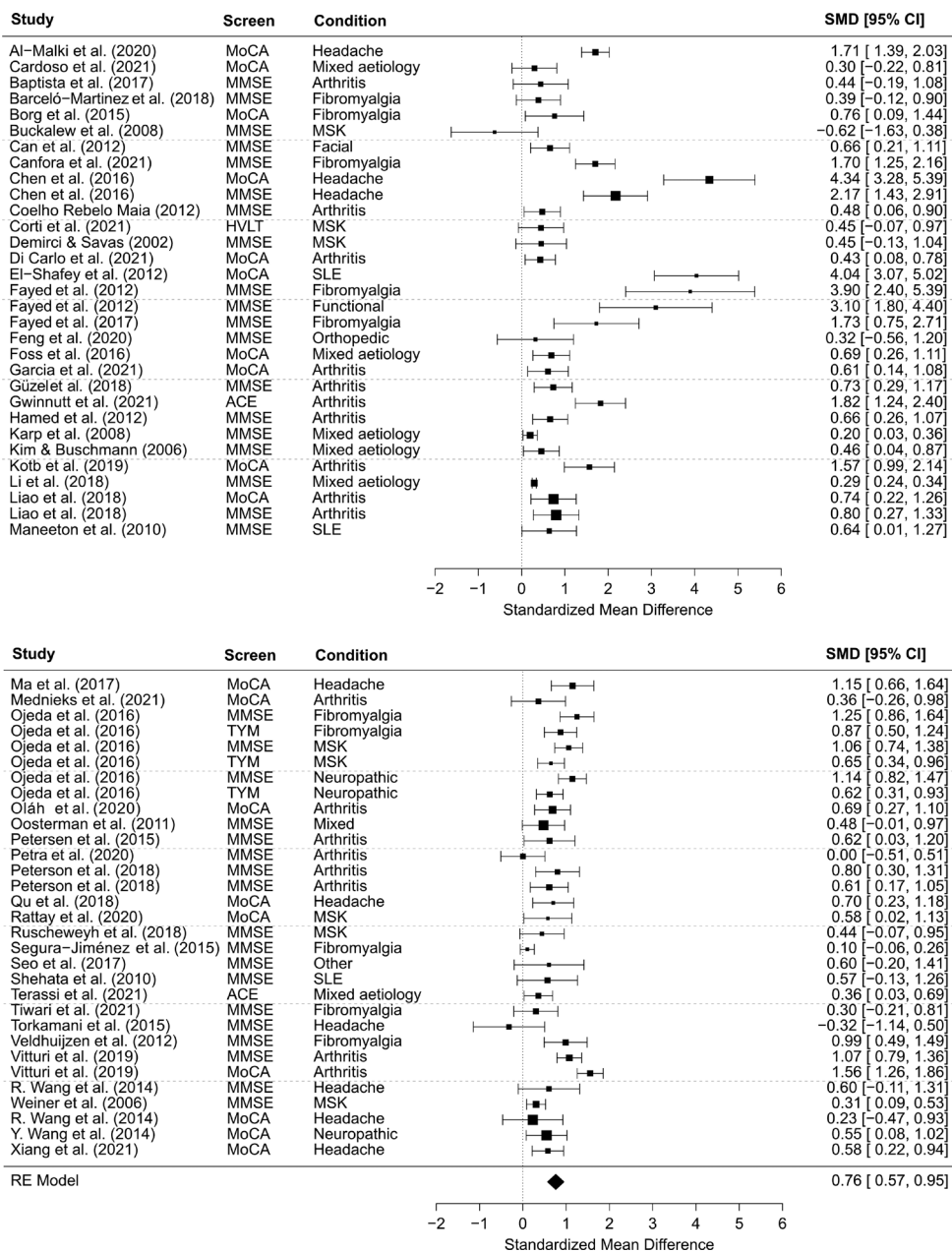


Figure 3. Forest plot. Depicts individual effects and pooled effects based on multi-level CHE model.

Effect sizes were larger for studies employing the MoCA (1.085, CI 0.624–1.546) than those using the MMSE (0.636, CI 0.445–0.826). For age comparisons, effects were larger for the young group (1.517, CI 1.007–2.028) than the old group (0.463, CI 0.075–0.851) and smaller still for the subset of these with the oldest samples (0.244, CI 0.119–0.368). When considering only groups where mood levels were

Table 2. Chronic pain status associations with cognitive screen performance.

Dataset	Meta-analytic method	<i>k</i>	<i>n</i>	SMD (95% confidence interval)	<i>p</i> -value	<i>I</i> ²	Within-cluster <i>I</i> ²	Between-cluster <i>I</i> ²
Total dataset	CHE	62	12991	0.760 [0.57–0.951]	<.001	93.16	34.59	58.57
Total dataset	RE	62	12991	0.827 [0.648–1.006]	<.001	94.00		
Low risk of bias	CHE	24	3070	0.667 [0.46–0.874]	<.001	81.23	29.38	51.85
Low risk of bias	RE	24	3070	0.693 [0.503–0.883]	<.001	81.00		
High risk of bias	CHE	38	9921	0.876 [0.534–1.218]	<.001	96.13	27.26	68.87
High risk of bias	RE	38	9921	0.961 [0.663–1.258]	<.001	96.00		
MMSE	CHE	37	10556	0.636 [0.445–0.826]	<.001	89.34	0	89.34
MMSE	RE	37	10556	0.7 [0.518–0.882]	<.001	90.00		
MoCA	RE	19	1692	1.085 [0.624–1.546]	<.001	94.00		
Arthritis	CHE	18	1746	0.751 [0.505–0.997]	<.001	74.57	22.9	51.68
Arthritis	RE	18	1746	0.782 [0.573–0.991]	<.001	74.00		
Fibromyalgia	CHE	10	1288	1.069 [0.39–1.747]	0.006	93.67	9.03	84.64
Fibromyalgia	RE	10	1288	1.052 [0.541–1.563]	<.001	92.00		
Headache	CHE	9	897	1.102 [0.075–2.128]	0.038	95.04	50.78	44.27
Headache	RE	9	897	1.21 [0.365–2.054]	0.005	95.00		
MSK	CHE	8	677	0.481 [0.175–0.788]	0.008	60.67	43.25	17.42
MSK	RE	8	677	0.518 [0.277–0.760]	<.001	61.00		
Matched depression	RE	8	428	0.532 [0.337–0.727]	<.001	0.00		
Young group	RE	20	1506	1.517 [1.007–2.028]	<.001	94.67		
Old group	RE	8	1489	0.463 [0.075–0.851]	0.0193	89.75		
Oldest group	RE	4	1132	0.244 [0.119–0.368]	0.0001	0.03		

Note. *k*=number of studies, *n*=number of data points, SMD=standardized mean difference, *I*²=heterogeneity statistic, decomposed into two levels (within each study and between each study) for the multi-level approach, RE=Random Effects, CHE=Correlated & Hierarchical Effects, MMSE=Mini-mental State Examination, MSK=musculoskeletal condition, MoCA=Montreal Cognitive Assessment, Young group=weighted mean age 36.3 & each study has M+1SD <55, Old group=weighted mean age 71.8 & each study has M-1SD <55, Older group=weighted mean age of 73.4 & each study has M-1SD <65.

explicitly matched, the estimated effect was 0.532 (CI 0.337–0.727). Forest plots for these comparisons can be found in [Appendix 5](#).

Study heterogeneity remained fairly high across these analyses except for two (mood-matched and oldest groups), where *I*² should be interpreted carefully as study numbers are small; values of zero occur in approximately a quarter of meta-analyses (von Hippel, 2015).

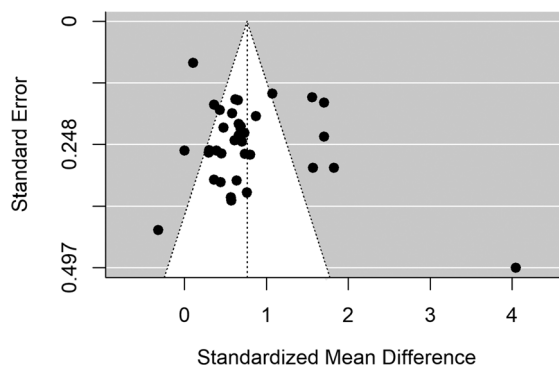


Figure 4. Funnel plot (focused studies).

Reporting biases

Figure 4 shows a funnel plot including studies where the cognitive screen was key to the study purpose. This uses the trim-and-fill method (Duval & Tweedie, 2000) to interpolate study effect sizes that would be expected from the extracted results, suggesting where low-powered and non-significant effects may be absent from the distribution. The plot suggests that no additional low-powered, non-significant effects would be expected given the observed distribution. The Egger test was conducted which seeks to identify a relationship between effect size and precision of estimate that may indicate systematic publication bias. The estimated coefficient was 1.35, $p = .18$, meaning the test cannot reject the null of no such relationship.

Discussion

Summary of findings

There appears to be considerable evidence for chronic pain being associated with lower scores on cognitive screens. For every analysis and sub-analysis, the 95% coverage interval did not include zero, suggesting that across diverse groups experiencing chronic pain, cognitive screen performance is lower than for control groups—even when low mood, which frequently co-occurs with pain, is similar across groups. However, the high levels of heterogeneity suggest that the sources of this effect may be manifold. Sub-analyses on the two most represented screens (MMSE and MoCA) saw some reduction of heterogeneity with larger effect sizes for comparisons involving the MoCA. The overall estimate for low risk of bias studies was 0.67 (95% CI 0.46–0.87).

Different pain conditions yielded slightly different pooled effects. The highest overall effect was for chronic headache/migraine sufferers; however, this effect had the 95% coverage interval which came closest to including zero. Fibromyalgia studies followed a similar pattern: a large point estimates with a wide confidence interval. The MSK group saw smaller effect sizes within again a wide confidence interval. The Arthritis sub-analysis demonstrated more consistency and an intermediate point estimate. We also note that the two studies (Karp et al., 2008; Terassi et al., 2021) explicitly limited to older adults (with low risk of bias) reported two of the three⁴ smallest SMDs.

Comparison with previous research

Pain conditions

For people living with arthritis, the current MA found similar effect sizes to those reported in Pankowski et al. (2022). The current arthritis sub-analysis excluded two studies from the Pankowski review due to rated high risk of bias - the MMSE study by Petersen et al. (2015) that excluded participants based on MMSE scores, and the MoCA study by Kotb et al. (2019) which lacked information about levels of education. The current sub-analysis included two further arthritis studies judged to have low risk of bias that were published after the prior review completed its searches.

Inflammatory diseases are increasingly understood to have neurological implications, meaning that patients with these conditions may score differently on cognitive screens because of pain and the direct action of the disease such as premature immunosenescence (Petersen et al., 2015). There is evidence, for instance, that patients with rheumatoid arthritis attain poorer MoCA scores than controls with similar levels of bodily pain (S. H. Kim et al., 2018). Similarly, brain changes are noted with chronic headache, for instance medication-overuse headache with increased white matter hyperintensity (Xiang et al., 2021) and changes in functional connectivity in the neostriatum (Z. Chen et al., 2016); however, note neurological changes need not result in an impact on cognition. Previous research has reported patients with fibromyalgia to have higher prevalence of cognitive deficit based on screen performance compared to other forms of pain (e.g. neuropathic or mixed pain, Rodríguez-Andreu et al., 2009), although score ranges do not differ drastically. We note also that the status of fibromyalgia is not settled and has been construed by some as a disorder with an origin in psychological distress rather than owing to physical causes, which may distinguish it from other conditions. However Häuser and Fitzcharles (2018) note that chronic primary pain was a category created precisely because "the etiology for many forms of chronic pain is unknown" (p. 55) and that fibromyalgia, while complex, appears to arise from a number of components rather than being simply an expression of somatic symptoms.

In this MA, the effects for musculoskeletal pain were lower than for other pain conditions. This may relate to severity of pain, which was not analyzed in this study. Q. Chen et al. (2011) reported that patients with self-reported musculoskeletal chronic pain who scored in the upper quartile on the Brief Pain Inventory Severity Scale were twice as likely as those in the lower quartile to obtain an MMSE score below 24 (18.5% vs 9.7%). However, Bosley et al. (2004) found no difference in MMSE scores between groups with significantly different pain intensity scores (MPQ-SF).

Cognitive scores

The larger effect sizes for the MoCA versus MMSE mirror what was reported by Pankowski et al. (2022). It is possible that there are true differential effects across these screens, driven by differences such as the lack of executive function assessment by the MMSE (Nieuwenhuis-Mark, 2010), as this is a core domain influenced by pain. However, the differences we observe may instead reflect the wider heterogeneity across studies, e.g. due to included pain conditions.

Limitations of evidence

The quality assessment found very few studies met every JBI criteria. In some cases, study design and decisions may not reflect poor quality *per se*; for instance, it may be appropriate to screen out lower scoring participants on screens for some study objectives. The infrequency of conducting pain measurements on control participants is understandable but prevents objective comparison of pain levels that could add more confidence to findings.

Most studies were uncontrolled for mood and medication differences between pain and control groups, which may reflect the realities of typical clinical samples: medication for the condition in question, and mood as understood to be a prevalent and co-occurring symptom with pain, forming part of a symptom cluster (Davis et al., 2016). Rock et al. (2014) report small to moderate effects of depression on cognition; however, a sub-analysis in the current meta-analysis involving groups with similar mood scores produced effect estimates broadly in line with that for all low risk of bias comparisons. Despite some statistical differences in mood scores by group, the SR dataset may not have contained a preponderance of individuals who would meet caseness for depression (and indeed some studies explicitly excluded participants on the basis of such diagnoses). Meanwhile, commonly prescribed medications for rheumatoid arthritis have been associated with cognitive impairment (on methotrexate, see Pamuk et al., 2013; on glucocorticoid therapy, see Coluccia et al., 2008). However, a study by Gogol et al. (2014) looked at the impact of opioid medication on MMSE performance and reported no effect.

Given that cognitive performance is known to be influenced by age and education, failure to match for these measures clearly introduces a risk of bias (although some studies may still mitigate this for their primary research question by controlling within a subsequent analysis of interest).

If pain were under-reported by people with cognitive impairment, this would introduce systematic error into the findings. There is evidence of such under-reporting for people with a dementia diagnosis (reviewed by Scherder et al., 2005); however, the current review excluded studies on that diagnosis or with similar neuropsychological impairments. Other research shows that less pronounced cognitive deficits are not associated with changes in pain perception or reporting (Docking et al., 2014; Kunz et al., 2009).

Limitations of review processes

This review focused on studies comparing pain and pain-free groups, meaning that it did not include longitudinal studies examining change over time or due to interventions, which could give insights into how cognitive screen performance follows the course of pain condition/fluctuation in pain experience. There was also insufficient specification of pain duration across studies to allow controlling for or investigating this factor, which is likely to be of interest given the parallels between chronic pain and neurodegenerative disease (Apkarian & Scholz, 2006).

This SR encompasses a range of diagnostic groups and samples without diagnosis (based on self-ratings), which is likely to contribute to the heterogeneity of the findings.

We felt it important to represent the range of forms of chronic pain that could arise for clinicians in the assessment of dementia and have conducted sub-analyses by condition where there was available data. As heterogeneity remained high when limiting analyses to a single cognitive screen, or to a single pain condition, the sources of heterogeneity are likely to include other factors that are difficult to model effectively using the available data, for instance impact of education, or severity of pain or of related factors such as sleep quality or depression. Heterogeneity did drop for two sub-analyses, involving matched depression and samples principally involving over-65s, but full interpretation of this is difficult due to the performance of I^2 for small study numbers.

Constraints on generality

This review chose to limit its cognitive screens to a fairly narrow list,⁵ to align with clinical usage. This list was made by UK clinicians and that this may limit generalizability. The Alzheimer's Association have produced a "Cognitive Assessment Toolkit," which uses the MMSE as a minimal reference point for detection validity and on that basis recommends two further measures as "equal or superior" (p. 3), the Mini-Cog and GP-COG (Alzheimer's Association, n.d). These tools are all referred to by the UK toolkit but the GP-COG is considered distinct from the cognitive screens, as it relies partly on informant report and as such is not purely a measure of current cognitive performance and was not included in our review. A survey of current primary care provider practices in the United States (Bernstein et al., 2019) reports the prevalence of cognitive screen usage, citing the MMSE and MoCA as examples, later noting that the MMSE and Mini-Cog are the assessments most frequently used by practitioners.

Cognitive screening tests can be defined in various ways and the UK practitioner toolkit takes a pragmatic approach focusing on function (detection validity). As a consequence, it includes both instruments that cover a range of cognitive domains (e.g. MMSE, MoCA), a few domains (Mini-COG) and a single domain (HVLIT and TYM). In the event, besides the MoCA and MMSE, there were very few studies extracted for the other cognitive screens, meaning that this review heavily focuses on these two measures. However, the studies included come from a range of countries including multiple from the Middle East, South America, and Asia, avoiding a focus merely on European and North American samples.

Meaning and future considerations

Given the association of effects of between half and one standard deviation poorer performance in chronic-pain experiencing participants, clinicians may wish to consider this when administering cognitive screens as part of a dementia investigation pathway. Based on point estimates from the low-risk of bias analysis (0.70), with normative data suggesting the major measures have standard deviations of around three or four (MMSE 3 - Tombaugh et al., 1996; MoCA 4 - Rossetti et al., 2011) into raw scores using normative data, we might plausibly see decrements of 2–2.70 points using these screens. However, it would be unwise to presume that a decrement purely reflects measurement error: for at least some conditions involving pain,

cognitive impairment may be a marker for later severe decline and development of dementia (Tian et al., 2023). It will be crucial to disentangle the dementia-uninformative and dementia-relevant components of such effects. In addition, future research should explore whether screen sub-domains differ in their sensitivity to chronic pain.

Notes

1. it was deemed unrealistic to expect mood and medication to be extricated from pain in most clinical samples; more detail in discussion section.
2. In one case, it was judged that groups could be more appropriately merged to produce a single standardised mean difference.
3. In most cases the cut-off employed (e.g. MMSE 24 or 28) fell within a 68% coverage interval of scores observed within our datasets; we exempted two cases where the threshold was very low and well outside this (e.g. MMSE 10 or 14) which removed only the severely cognitively impaired as part of exclusion criteria.
4. with Torkamani et al. (2015).
5. In preparation for this review, the first author collated a list of over 100 measures described across systematic reviews of cognitive screens.

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