How is the prediction of dementia using cognitive scores affected by comorbid pain?

Alexander Fradera, BSc, PhD

Submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology

Institute of Health and Wellbeing

College of Medical, Veterinary and Life Sciences

University of Glasgow

July 2022

Table of Contents

List of Tables

Systematic Review

Major Research Project

List of Figures

Systematic Review

Major Research Project

Acknowledgements

I owe deep gratitude to my academic supervisors, Lisa Gadon, Jon Evans, and Breda Cullen for managing a project that evolved in bursts and a student who needed support, inspiration, and now and then, a little corralling. Similarly, to Jess Fish for continued encouragement. It was great to share review duties with someone as sharp, thorough and considerate as Jess McLaren. Paul Cannon and Robin Young were also gracious with their time and advice. I've also felt very lucky to have been supported by total strangers in the form of NHS R Community Slack, StackExchange and countless free blogs, vignettes and manuals.

My clinical supervisors have all been massively supportive across the years but in particular I am grateful to Leigh Whitnall for canny guidance and a truly reflective space. I similarly want to acknowledge Kate O'Reilly and Katy Woodward at the RVI for their motivation and support of me on my journey into the DClin, and Michael Kopelman for first opening the road into clinical research.

Despite the fissures that the pandemic carved into all our lives, I am lucky to have weathered it with this cohort and my friends and family in games or conversation. And to have spent it with a household of supporters - above all Kathryn, who has met me with kindness, understanding and humour all along the way.

Chapter 1: Systematic Review

Does the presence of chronic pain affect scores on cognitive screening tests/brief cognitive measures? A Systematic Review

Prepared in accordance with the author requirements for the journal Psychological Medicine
https://www.cambridge.org/core/journals/psychological-medicine/information/instructions-contributors

Abstract

Chronic pain is increasingly prevalent with age and impairs cognitive function, but it is not known if it can affect performance on cognitive screening tests commonly used to detect dementia. This systematic review and meta-analysis (SR/MA) aimed to assess this question. PRISMA guidelines were followed. Studies were included with participants age >18 with a pain-free control group and at least one chronic-pain group defined as self-reported pain lasting >3 months or a diagnosis included in lists curated by the International Association for the Study of Pain. Embase (Ovid), Medline, PsycINFO (September 2021) and OpenGrey (January 2021) were searched. Risk of bias was assessed using the Joanna Briggs Critical Appraisal Checklist for Cross-Sectional Studies. Due to clustering of effects (multiple effects extracted from studies) a random effects multilevel modelling approach was used to calculate Hedges' g with positive g reflecting impairment in the chronic pain group. 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 (I^2 = 93.16%) with some reductions in sub-analyses. Around half of studies were identified as being at a low risk of bias. There was no evidence of publication bias. Study bias factors limit interpretation of the findings as a whole, but sub-analyses suggest real effects exist within different pain conditions, for different screening measures, and that pain should be considered when cognitive screens are employed.

Introduction

Rationale

Cognitive screening tools are measures designed to detect cognitive impairment through brief means, typically within 20 minutes (Cullen, O'Neill, Evans, Coen, and Lawlor, 2007). These target either one highly predictive ability or core domains (e.g. language, memory, attention) using a minimal set of items. While cognitive screening is used for many conditions such as brain tumours, 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, which is typically time-intensive and cognitively demanding. Cognitive screens should thus be sufficiently sensitive - correctly identifying when followup 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. 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, Scior, Mandy, and Charlesworth, 2017), other frequently used screens such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) show an influence of intelligence (Alves, Simões, Martins, Freitas, and Santana, 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, Marchuk, and Pichora-Fuller (2016) reporting a three-point decrement on the MoCA when completing the measure under noisy conditions. Accuracy 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 or thinking (McCracken and 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, McGuire, and Finn (2011).

These authors note that potential mechanisms behind this performance impact 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), it is 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, Wytrychiewicz-Pankowska, Janowski, and Pisula (2022) present meta-analyses showing cognitive impairment across several domains, and Meade, Manolios, Cumming, Conaghan, and Katz (2018) note impairments particularly in memory, attention and verbal function. A review of fibromyalgia by Schmidt-Wilcke, Wood, and Lürding (2010) summarises 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 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 standardised 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 cognitive screen performance. However, this may not generalise 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.

Method

The study followed the PRISMA guidelines for reporting SRs and MAs (Moher, Liberati, Tetzlaff, Altman, and PRISMA Group, 2009). The protocol of the study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [registration number: CRD 42021272835] and published elsewhere (https://osf.io/jsqxn/). The protocol was updated 14th May 2021 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 was 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 utilised 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 (HVLT), 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 5th April 2021. Searches of bibliographic databases were conducted on 17th 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 operationalised in title and abstract by identification of key pain-related conditions (fibromyalgia, arthritic and rheumatic conditions), chronic adj/5 pain or headache/migraine, or report of a standardised 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 operationalised 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 A1 (pp. 88-93).

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 two 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 one. AF completed the full text review on all remaining results. Authors were contacted when full articles are 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 three 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 and Bogduk, 1994, lists 1A, 1F, 1H). Full guidelines for reviewers for both title-abstract and full-text screening can be found in Appendix A2 (pp. 94-98).

Data extraction and items

Data was 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 was provide on multiple outcomes (cognitive screens) all outcomes were extracted. A data dictionary can be found in Appendix A3 (p. 108).

Quality assessment tool

Study quality was assessed using the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (Moola S and P-F., 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 A4 (p. 109). 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 education[1]; 7) reporting information about screen administration; 8) appropriate screen data available without floor effects introduced by a cognitive screen cut-off. No overall risk of bias score is produced using this tool. Reviewers AF and JM independently reviewed quality for five studies before meeting to resolve discrepancies and use this to amend the supplementary guidance for further quality assessment, which was completed by AF.

Statistical analyses - effect measures and synthesis

Cognitive screen means and standard deviations were used to compute standardised mean differences (SMD) in the form of Hedge's 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 was 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 visualised using forest plots. A multi-level

[1] it was deemed unrealistic to expect mood and medication to be extricated from pain in most clinical samples; more detail in discussion section.

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 standardised mean differences per study[2]. This produces interdependency between outcomes, which was 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 A5 (pp. 110-117). Two types of sub-group analysis were considered: those focusing on data from a single cognitive screening measure, and those involving data from a single pain condition. These analyses were attempted for situations where five or more comparisons were available. Analysis code is available on Appendix A3 (p. 108).

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

[2] In one case, it was judged that groups could be more appropriately merged to produce a single standardised mean difference.

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, Buchman, Arfanakis, Fleischman, and Bennett, 2013) that did explicitly report a chronic pain group but using a minimum duration of one 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, leading 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 7054 people experiencing chronic pain and 5917 pain-free controls was extracted. There were 37 comparisons involving the MMSE, 19 for the MoCA, 3 for the TYM, 2 for the ACE, and 1 for the HVLT. 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 the studies.

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 the majority of comparisons failed to meet either criteria 3 (k = 46) or 5 (k =39) due respectively to lack of pain measurement in both control and pain groups and non-reporting of mood, education, age or medication information. Half of comparisons (k = 31) 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[3].

The decision was made to consider studies with low risk of bias as those meeting these criteria:

- adequate exclusion criteria (J1)
- controlled or matched for age and education (J6)
- did not employ a cut-off that prevented detection of poor performance (J-8)

This resulted in 23 comparisons with a low risk of bias.

---

[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.

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 on 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 = 481.9, p < 0.0001). The estimated variance components were τ^2_{Level} = 0.251 and τ^2_{Lev} = 0.148, 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, and from these comparisons sub-analyses were conducted with i) MMSE screen only ii) MoCA screen only iii) arthritis pain condition only, employing the multi-level approach when the data-set contained clusters and iv) a stronger test of effects within low-risk of bias situations with only comparisons where groups had similar levels of mood. Sub-analyses are presented for the other major pain conditions (fibromyalgia, headache and musculoskeletal conditions), but note that these contain high- and low-risk of bias comparisons as too few comparisons were otherwise available. For comparison an analysis with high risk of bias studies is included in the table. Study heterogeneity remained fairly high across these analyses except for the one focused on comparable mood scores, where I^2 should be interpreted carefully as study numbers are small (Hippel, 2015). These are reported in Table 2.

Reporting biases

Fig 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 and 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, providing no evidence of reporting biases.

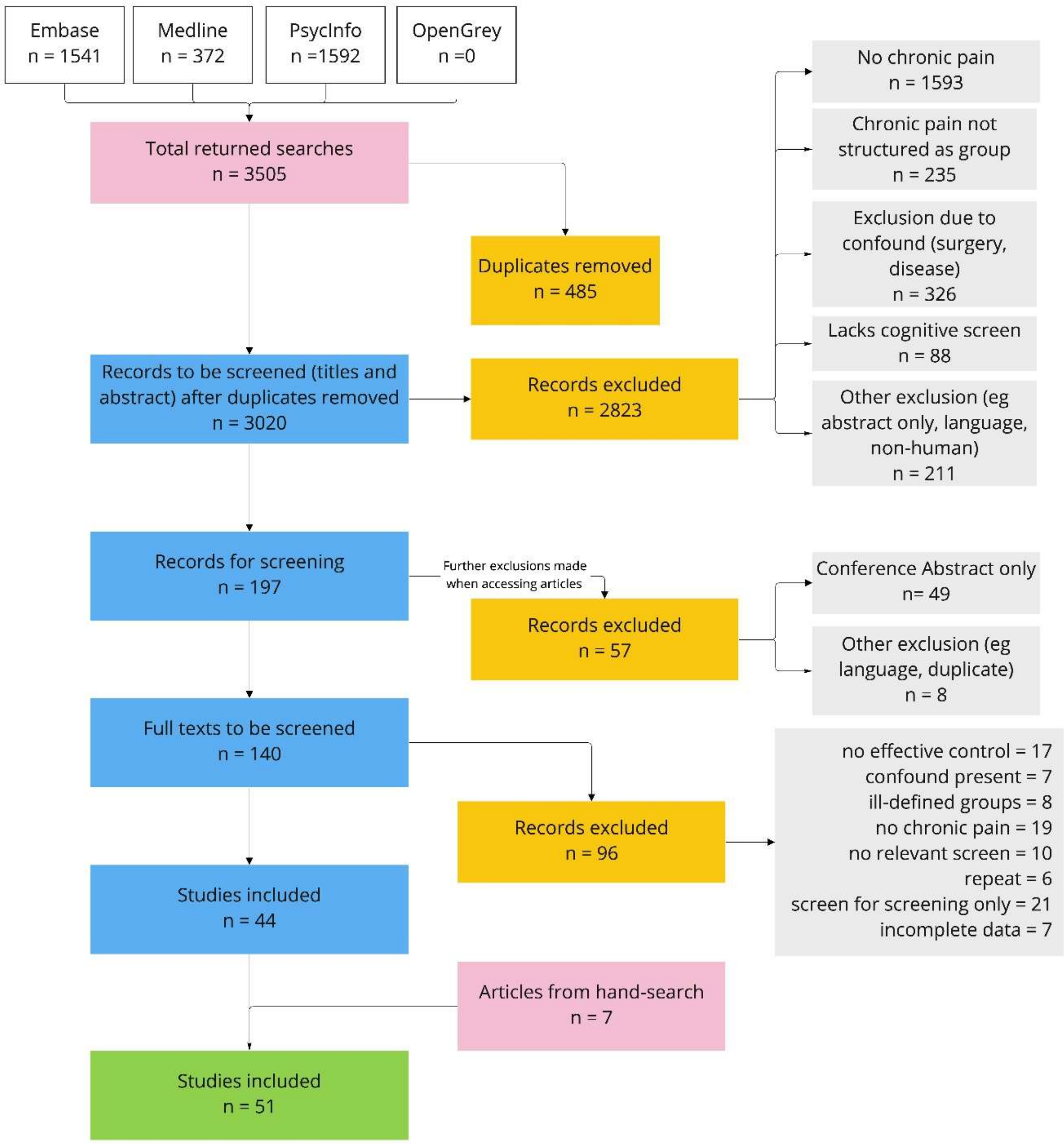


Fig 1. PRISMA flow diagram

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Al-Malki, Kotb, Kamal, Abd El Fatah, and Ahmed (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
Boldt et al. (2020)	Germany	Hereditary spastic paraplegia	16	higher for controls	50.6 (9.5)	MoCA
Borg, Emond, Colson, Laurent, and Michael (2015)	USA	Fibromyalgia	18	higher for controls	50.39 (9.87)	MoCA
Buckalew, Haut, Morrow, and Weiner (2008)	USA	Older adults self-reporting chronic lower back pain	8	no sig diff	74.5 (4.2)*	MMSE
Can, Gencay-Can, and Gunendi (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
Chen et al. (2016)	China	Chronic migraine	16	higher for controls	42.4 (8.7)	MoCA

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
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, Gasson, and Loftus (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, Abd-El-Geleel, and Soliman (2012)	Egypt	SLE	30	no sig diff	34.56 (6.01)	MoCA
N. Fayed et al. (2012)	Spain	Fibromyalgia	10	not reported	38.94 (5.56)	MMSE
N. Fayed et al. (2012)	Spain	Somatisation disorder	10	not reported	43.92 (9.96)	MMSE
Nicolás Fayed, García-Martí, Sanz-Requena, Marti-Bonmatí, and Garcia-Campayo (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

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Foss, Ferreira, Oliver, Thomaz, and Teixeira (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, Rudy, and Weiner (2008)	USA	Older adults with self-reported pain	476	no sig diff	73.4 (5.9)	MMSE
Kim and Buschmann (2006)	Korea	Older adults with self-reported pain	85	higher for patients	72.85 (5.42)[†]	MMSE
Kotb, El Attar, Elabd, El Nagger, and Maabady (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

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Liao et al. (2018)	China	Knee osteoarthritis	30	not reported	56.5 (6.8)	MMSE
Ma et al. (2017)	China	Medication overuse headache	44	not reported	42.3 (9.62)	MoCA
Maneeton, Maneeton, and Louthrenoo (2010)	Thailand	SLE - no CNS involvement	19	no sig diff	31.3 (8.2)	MMSE
Mednieks, Naumovs, and Skilters (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
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

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Oláh et al. (2020)	Hungary	Rheumatoid Arthritis	60	no sig diff	60.7 (9.5)	MoCA
Oosterman, Derksen, Wijck, Veldhuijzen, and Kessels (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, Yu, Xia, and Chen (2018)	China	Chronic tension-type headache	51	no sig diff	37.6 (12.6)	MoCA
Ruscheweyh, Fritz, Eggert, Azad, and Straube (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

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Shehata, Abdel-Kareem, El Adl, and Yassin (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, Sondaal, and Oosterman (2012)	Netherlands	Fibromyalgia	35	higher for controls	30.4 (8.6)	MMSE
Vitturi, Nascimento, Alves, de Campos Sobolewski Carneiro, and Torigoe (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 (NR)	MoCA
R. Wang et al. (2014)	China	Cluster headache	17	not reported	35.4 (NR)	MMSE
Y. Wang et al. (2014)	China	Idiopathic trigeminal neuralgia	36	no sig diff	56.4 (8.49)	MoCA

Table 1. Characteristics of studies

Authors	Country	Pain group	Patient group size	Education	Patient age - Mean (SD)	Screen
Weiner, Rudy, Morrow, Slaboda, and Lieber (2006)	USA	Chronic lower back pain	163	no sig diff	73.6 (5.2)	MMSE
Xiang, Chen, Lin, Xiong, and Zheng (2021)	China	Medication overuse headache	88	no sig diff	50.01 (14.49)	MoCA

MSK = Musculo-skeletal condition. SLE = Systemic Lupus Erythematosus. Test abbreviations: 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 all reported significant age differences but age data did not allow extraction of a mean and standard deviation.

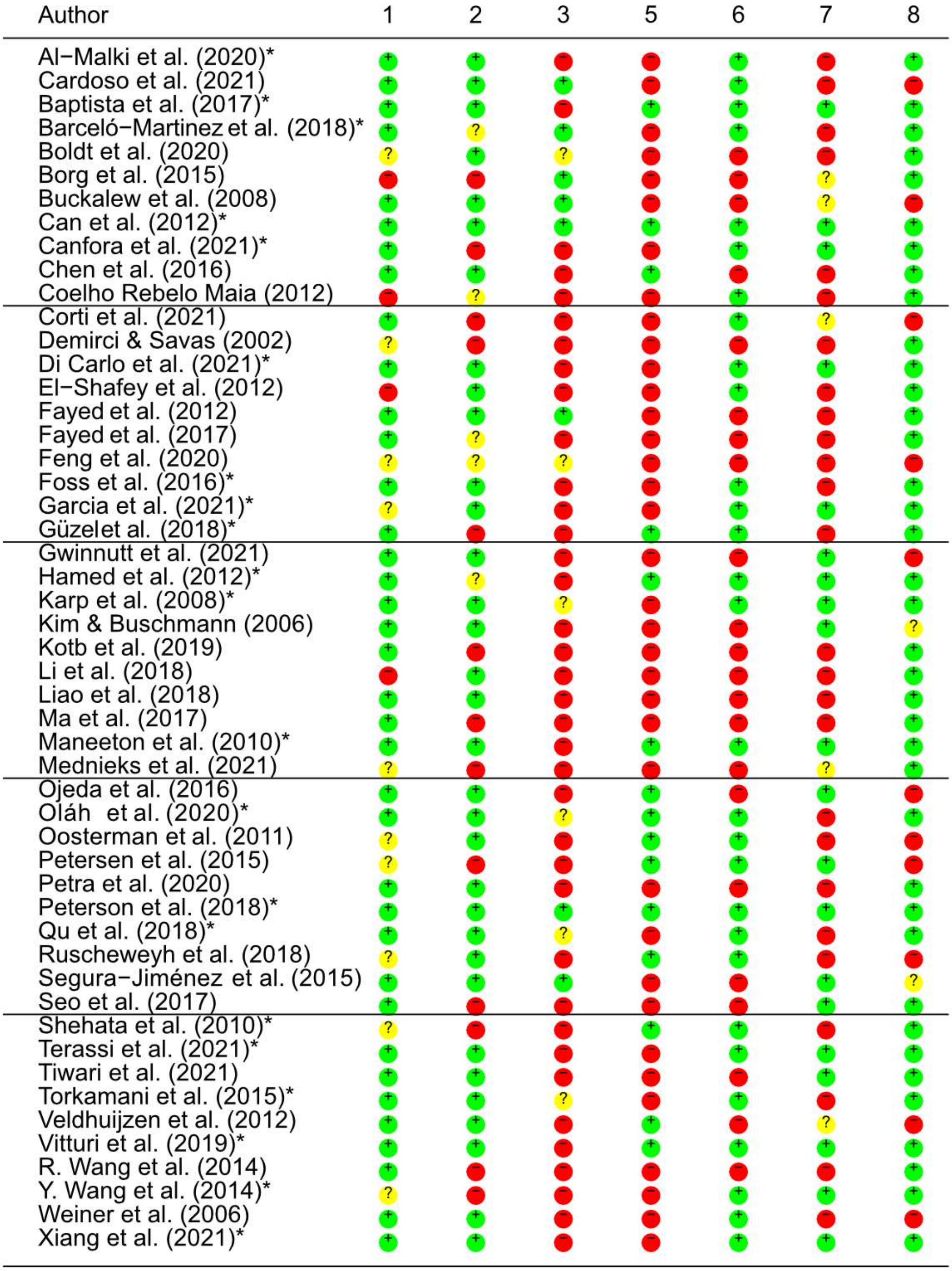


Fig 2. Risk of bias plot. Asterisks denote those determined to have low risk of bias.

Column numbers are JBI items.

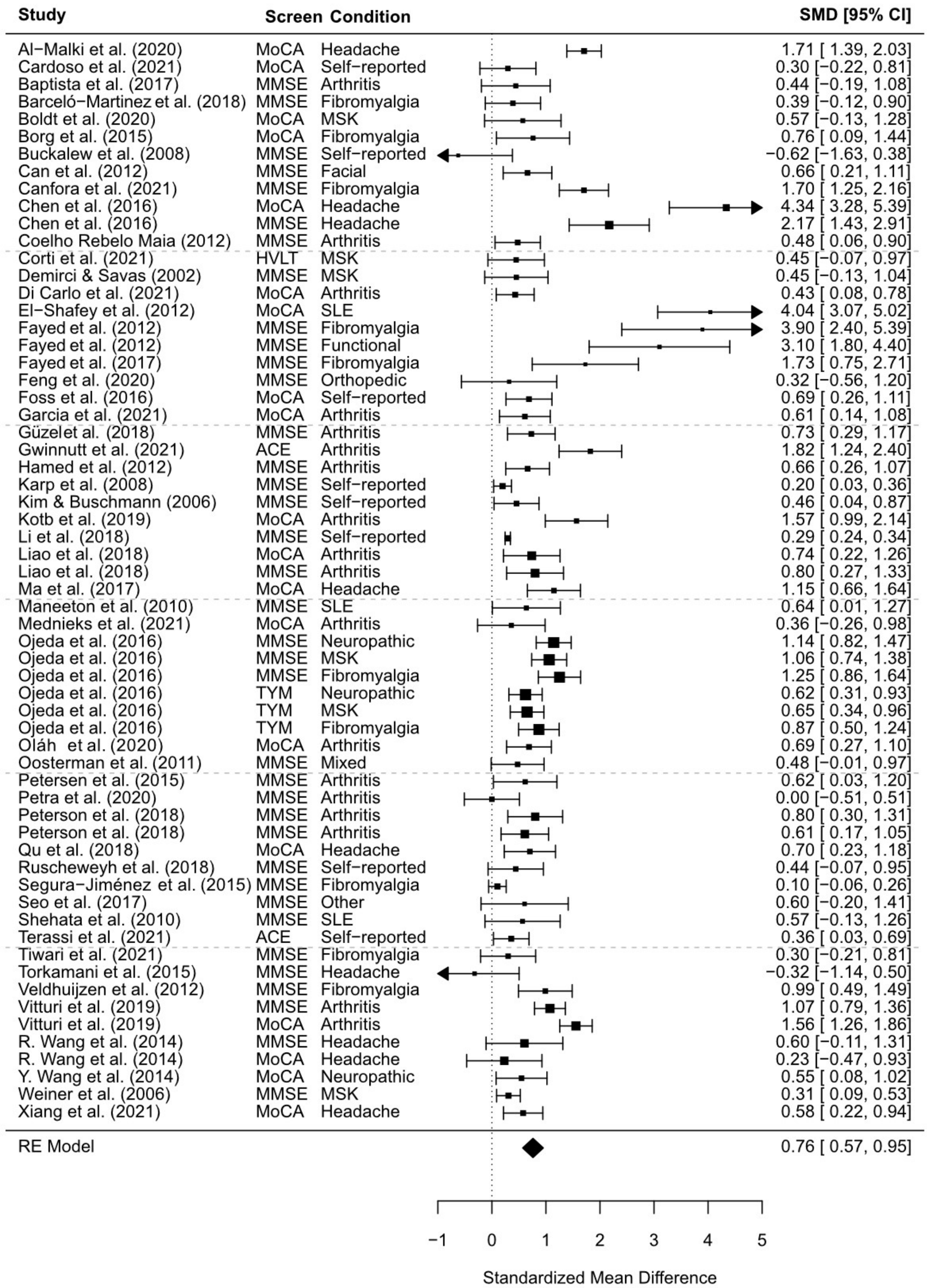


Fig 3. Forest plot. Depicts individual effects and pooled effects based on multi-level CHE model.

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

Dataset	**Meta-analytic method**	***k***	***n***	**SMD [95% confidence interval]**	**p-value**	***I*²**	**Within- cluster *I*²**	**Between- cluster *I*²**
Total dataset	CHE	62	12,971	0.761 [0.57 - 0.951]	< .001	93.16	34.53	58.63
Total dataset	RE	62	12,971	0.827 [0.648 - 1.006]	< .001	94.00		
Low risk of bias	CHE	23	3,011	0.697 [0.49 - 0.904]	< .001	80.57	31.04	49.52
Low risk of bias	RE	23	3,011	0.722 [0.533 - 0.912]	< .001	81.00		
High risk of bias	CHE	39	9,960	0.846 [0.511 - 1.181]	< .001	96.05	27.19	68.86
High risk of bias	RE	39	9,960	0.935 [0.642 - 1.229]	< .001	96.00		
MMSE	CHE	13	1,686	0.65 [0.359 - 0.942]	< .001	78.13	0	78.13
MMSE	RE	13	1,686	0.658 [0.415 - 0.902]	< .001	76.00		
Arthritis	CHE	10	1,262	0.743 [0.46 - 1.027]	< .001	68.16	37	31.17
Arthritis	RE	10	1,262	0.789 [0.556 - 1.021]	< .001	70.00		

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

Dataset	Meta-analytic method	*k*	*n*	SMD [95% confidence interval]	p-value	I^2	Within- cluster I^2	Between- cluster I^2
Fibromyalgia	CHE	10	1,288	1.069 [0.39 - 1.747]	0.006	93.67	9.03	84.64
Fibromyalgia	RE	10	1,288	1.052 [0.541 - 1.563]	< .001	92.00		
MSK	CHE	8	877	0.476 [0.159 - 0.792]	0.009	61.07	42.18	18.88
MSK	RE	8	877	0.515 [0.266 - 0.764]	< .001	61.00		
Headache	CHE	9	677	1.102 [0.075 - 2.128]	0.038	95.04	50.78	44.27
Headache	RE	9	677	1.21 [0.365 - 2.054]	0.005	95.00		
MoCA	RE	9	1,176	0.85 [0.532 - 1.167]	< .001	83.00		
Matched depression	RE	4	264	0.699 [0.45 - 0.948]	< .001	0.00		

k = number of studies, *n* = number of data points, SMD = standardised 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 and Hierarchical Effects, MMSE = Mini-mental State Examination, MSK = musculoskeletal condition, MoCA = Montreal Cognitive Assessment

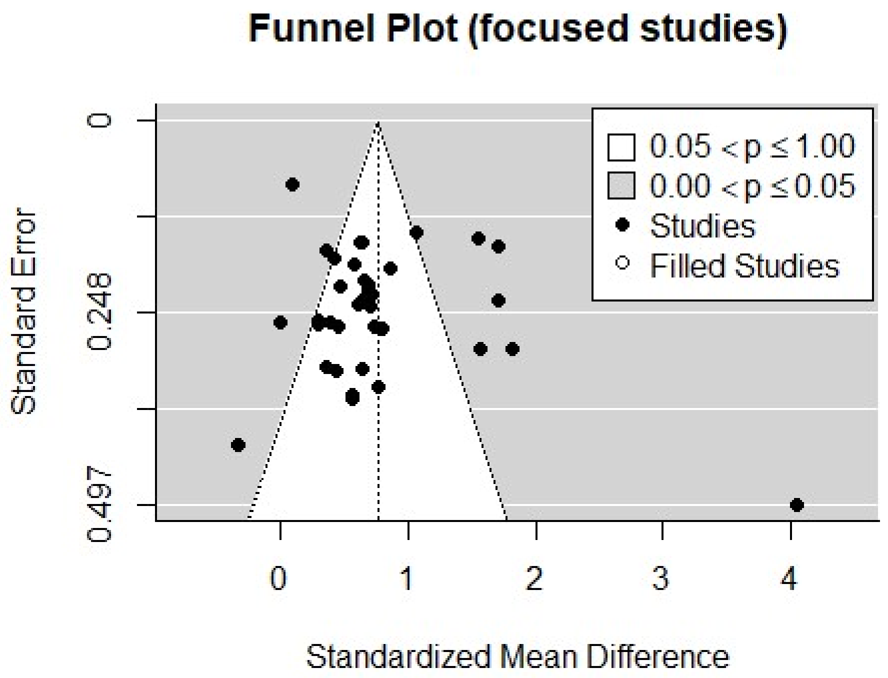


Fig 4. Funnel plot.

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, and saw larger effect sizes for the MoCA, suggesting that the screens may be differentially affected by chronic pain. The overall estimate for low risk of bias studies was 0.697 (95% CI 0.49 - 0.904).

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. Note that these analyses included studies at a high risk of bias, which as a whole produced higher point estimates and wider coverage intervals than studies with a low risk of bias. Studies (limited to low risk of bias) on arthritis 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 three[4] smallest SMDs.

Comparison with previous research

Pain conditions

For people living with arthritis, Pankowski et al. (2022) found effect sizes similar to those in the current analysis. In both cases estimates were based on small numbers of studies (studies/comparisons: Pankowski MMSE = 7/8, MoCA 3/3, current study MMSE 5/7, MoCA 4/4) and this MA excluded two MMSE comparisons and one MoCA comparison included in their analyses due to risk of bias. 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

---

[4] with Torkamani et al. (2015).

do not differ drastically. 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 analysed in this study. Q. Chen, Hayman, Shmerling, Bean, and Leveille (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% versus 9.7%). However, Bosley, Rudy, Granieri, and Weiner (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 that found by Pankowski et al. (2022). One reason for this may be because the MMSE does not draw on executive function in its assessment (Nieuwenhuis-Mark, 2010), which is a domain known to be influenced by pain.

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, Kroenke, Monahan, Kean, and Stump, 2016). Rock, Roiser, Riedel, and Blackwell (2014) report small to moderate effects of depression on cognition; however a sub-analysis where groups had 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, Hartmann, Wustmann, and Simm (2014) looked at the impact of opioidal 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 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; see e.g. Kunz, Mylius, Schepelmann, and Lautenbacher, 2009).

Limitations of review processes

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.

In addition, 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 generalisability. Moreover, besides the MoCA and MMSE, there were very few studies extracted for the other cognitive screens, meaning that this review heavily focuses on just 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.

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

[5] In preparation for this review, the first author collated a list of over 100 measures described across systematic reviews of cognitive screens.

interventions, which could give insights into how cognitive screen performance follows the course of pain condition/fluctuation in pain experience.

Meaning and implications

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. Normative data suggests that in groups with no cognitive impairment, MMSE SD is around three points (Tombaugh, McDowell, Kristjansson, and Hubley, 1996) meaning that a typical decrement of 2 [95% CI 1.1 - 2.8] points is a plausible estimate. The larger effects for the MoCA tool would (based on norms in Rossetti, Lacritz, Cullum, and Weiner, 2011 suggesting SD of 4) equate to 3.4 [95% CI 2.1 - 4.7] points. Crucial to consider however is whether for at least some conditions involving pain, cognitive impairment may be a marker for later severe decline. Future research should explore screen performance by sub-domains, to identify if there are certain areas where pain impacts and others where it does not affect results.

Declaration of interest

None.

References

Al-Malki, D., Kotb, M. A., Kamal, A. M., Abd El Fatah, A. S., & Ahmed, Y. M. (2020). Cognitive performance in patients with chronic tension-type headache and its relation to neuroendocrine hormones. *Egyptian Journal of Neurology, Psychiatry and Neurosurgery*, *56*(1), 16. https://doi.org/10.1186/s41983-020-0150-3

Alves, L., Simões, M. R., Martins, C., Freitas, S., & Santana, I. (2013). Premorbid IQ influence on screening tests' scores in healthy patients and patients with cognitive impairment. *Journal of Geriatric Psychiatry and Neurology*, *26*(2), 117–126. https://doi.org/10.1177/0891988713484194

Alzheimer's Society. (2013). *Helping you to assess cognition: A practical toolkit for clinicians*. Alzheimer's Society. Retrieved from Alzheimer's Society website: https://www.alz.org/getmedia/9687d51e-641a-43a1-a96b-b29eb00e72bb/cognitive-assessment-toolkit

Ashford, J. W. (2008). Screening for memory disorders, dementia and Alzheimer's disease. *Aging Health*, *4*(4), 399–432. https://doi.org/10.2217/1745509X.4.4.399

Baptista, T. S. A., Petersen, L. E., Molina, J. K., Nardi, T. de, Wieck, A., Prado, A. do, … Bauer, M. E. (2017). Autoantibodies against myelin sheath and S100β are associated with cognitive dysfunction in patients with rheumatoid arthritis. *Clinical Rheumatology*, *36*(9), 1959–1968. https://doi.org/10.1007/s10067-017-3724-4

Barceló-Martinez, E., Gelves-Ospina, M., Lechuga, E. N., Allegri, R. F., Orozco-Acosta, E., Benítez-Agudelo, J. C., … Román, N. F. (2018). Serum cortisol levels and neuropsychological impairments in patients diagnosed with fibromyalgia. *Actas Españolas de Psiquiatría*, *46*(1), 1–11. Retrieved from https://pubmed.ncbi.nlm.nih.gov/29417976/

Berryman, C., Stanton, T. R., Bowering, K. J., Tabor, A., McFarlane, A., & Moseley, G. L. (2013). Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain*, *154*(8), 1181–1196. https://doi.org/10.1016/j.pain.2013.03.002

Berryman, C., Stanton, T. R., Bowering, K. J., Tabor, A., McFarlane, A., & Moseley, G. L. (2014). Do people with chronic pain have impaired executive function? A meta-analytical review. *Clinical Psychology Review*, *34*(7), 563–579. https://doi.org/10.1016/j.cpr.2014.08.003

Boldt, A., Volker, M., Rattay, T. W., Wiethoff, S., Hengel, H., Schule, R., & Schols, L. (2020). Non-motor symptoms are relevant and possibly treatable in hereditary spastic paraplegia type 4 (SPG4). *Clinical Neurophysiology*, *131*(4), e209. https://doi.org/10.1016/j.clinph.2019.12.065

Borg, C., Emond, F. C., Colson, D., Laurent, B., & Michael, G. A. (2015). Attentional focus on subjective interoceptive experience in patients with fibromyalgia. *Brain and Cognition*, *101*, 35–43. https://doi.org/10.1016/j.bandc.2015.10.002

Bosley, B. N., Rudy, T. E., Granieri, E., & Weiner, D. K. (2004). Is chronic nonmalignant pain associated with decreased appetite in older adults? Preliminary evidence. *Journal of the American Geriatrics Society*, *52*(2), 247–251. https://doi.org/10.1111/j.1532-5415.2004.52063.x

Buckalew, N., Haut, M. W., Morrow, L., & Weiner, D. (2008). Chronic pain is associated with brain volume loss in older adults: Preliminary evidence. *Pain Medicine*, *9*(2), 240–248. https://doi.org/10.1111/j.1526-4637.2008.00412.x

Can, S. S., Gencay-Can, A., & Gunendi, Z. (2012). Validity and reliability of the clock drawing test as a screening tool for cognitive impairment in patients with fibromyalgia. *Comprehensive Psychiatry*, *53*(1), 81–86. https://doi.org/10.1016/j.comppsych.2011.02.001

Canfora, F., Calabria, E., Marenzi, G., Gasparro, R., Pecoraro, G., Mignogna, M. D., … D'Aniello, L. (2021). Burning fog: Cognitive impairment in burning mouth syndrome. *Frontiers in Aging Neuroscience*, *13*, 727417. https://doi.org/10.3389/fnagi.2021.727417

Cardoso, J., Apagueno, B., Lysne, P., Hoyos, L., Porges, E., Riley, J. L., … Cruz-Almeida, Y. (2021). Pain and the Montreal Cognitive Assessment (MoCA) in aging. *Pain Medicine (Malden, Mass.)*, *22*(8), 1776–1783. https://doi.org/10.1093/pm/pnab003

Chen, Q., Hayman, L. L., Shmerling, R. H., Bean, J. F., & Leveille, S. G. (2011). Characteristics of chronic pain associated with sleep difficulty in older adults: The maintenance of balance, independent living, intellect, and zest in the elderly (MOBILIZE) Boston study. *Journal of the American Geriatrics Society*, *59*(8), 1385–1392. https://doi.org/10.1111/j.1532-5415.2011.03544.x

Chen, Z., Chen, X., Liu, M., Liu, S., Shu, S., Ma, L., & Yu, S. (2016). Altered functional connectivity of the marginal division in migraine: A resting-state fMRI study. *The Journal of Headache and Pain*, *17*.

Coelho Rebelo Maia, L. A. (2012). The impact of rheumatoid arthritis in neuropsychology, depression and anxiety. A case control study, with 90 Portuguese female subjects. *Revista Ecuatoriana de Neurologia*, *21*(1-3), 55–60. Retrieved from http://revecuatneurol.com/magazine_issue_article/the-impact-of-rheumatoid-arthritis-in-neuropsychology-depression-and-anxiety-case-control-study/

Coluccia, D., Wolf, O. T., Kollias, S., Roozendaal, B., Forster, A., & Dominique, J.-F. (2008). Glucocorticoid therapy-induced memory deficits: Acute versus chronic effects. *Journal of Neuroscience*, *28*(13), 3474–3478. https://doi.org/10.1523/JNEUROSCI.4893-07.2008

Corti, E. J., Gasson, N., & Loftus, A. M. (2021). Cognitive profile and mild cognitive impairment in people with chronic lower back pain. *Brain and Cognition*, *151*. https://doi.org/10.1016/j.bandc.2021.105737

Cullen, B., O'Neill, B., Evans, J. J., Coen, R. F., & Lawlor, B. A. (2007). A review of screening tests for cognitive impairment. *Journal of Neurology, Neurosurgery, and Psychiatry*, *78*(8), 790–799. https://doi.org/10.1136/jnnp.2006.095414

Davis, L. L., Kroenke, K., Monahan, P., Kean, J., & Stump, T. E. (2016). The SPADE symptom cluster in primary care patients with chronic pain. *The Clinical Journal of Pain*, *32*(5), 388–393. https://doi.org/10.1097/AJP.0000000000000286

Demirci, S., & Savas, S. (2002). The auditory event related potentials in episodic and chronic pain sufferers. *European Journal of Pain*, *6*(3), 239–244. https://doi.org/10.1053/eujp.2001.0342

Di Carlo, M., Becciolini, A., Incorvaia, A., Beci, G., Smerilli, G., Biggioggero, M., … Salaffi, F. (2021). Mild cognitive impairment in psoriatic arthritis: Prevalence and

associated factors. *Medicine*, *100*(11), e24833.
https://doi.org/10.1097/MD.0000000000024833

Docking, R. E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G. J., & Jones, G. T. (2014). Pain reporting in older adults: The influence of cognitive impairment - results from the Cambridge City >75 cohort study. *British Journal of Pain*, *8*(3), 119–124. https://doi.org/10.1177/2049463714527437

Dupuis, K., Marchuk, V., & Pichora-Fuller, M. (2016). Noise affects performance on the Montreal Cognitive Assessment. *Canadian Journal on Aging*, *35*(3), 298–307. https://doi.org/10.1017/S0714980816000313

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot–based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*(2), 455–463. https://doi.org/10.1111/j.0006-341x.2000.00455.x

El-Shafey, A., Abd-El-Geleel, S. M., & Soliman, E. S. (2012). Cognitive impairment in non-neuropsychiatric systemic lupus erythematosus. *Egyptian Rheumatologist*, *34*(2), 67–73. https://doi.org/10.1016/j.ejr.2012.02.002

Fayed, N., Andres, E., Rojas, G., Moreno, S., Serrano-Blanco, A., Roca, M., & Garcia-Campayo, J. (2012). Brain dysfunction in fibromyalgia and somatization disorder using proton magnetic resonance spectroscopy: A controlled study. *Acta Psychiatrica Scandinavica*, *126*(2), 115–125. https://doi.org/10.1111/j.1600-0447.2011.01820.x

Fayed, Nicolás, García-Martí, G., Sanz-Requena, R., Marti-Bonmatí, L., & Garcia-Campayo, J. (2017). Difference in regional brain volume between fibromyalgia patients and long-term meditators. *Actas Españolas de Psiquiatría*, *45*(6), 268–276. Retrieved from https://pubmed.ncbi.nlm.nih.gov/29199761/

Feng, S., Li, B., Li, G., Hua, X., Zhu, B., Li, X., … Xu, J. (2020). Abnormal spatial patterns of intrinsic brain activity in osteonecrosis of the femoral head: A resting-state functional magnetic resonance imaging study. *Frontiers in Human Neuroscience*, *14*. https://doi.org/10.3389/fnhum.2020.551470

Foss, M. P., Ferreira, K. D. S., Oliver, G. Z., Thomaz, D. C., & Teixeira, C. T. (2016). Cognitive deficits in chronic pain patients, in a brief screening test, are independent of comorbidities and medication use. *Arquivos de Neuro-Psiquiatria*, *74*(5), 361–366. https://doi.org/10.1590/0004-282X20160071

Garcia, L. O. K. L., Junior, A. T. S., Santos Gomez, D. C. dos, Yoshikawa, G. S. S., Kamikoga, C. K., & Vitturi, B. K. (2021). Cognitive impairment in patients with psoriatic arthritis. *Acta Neurologica Belgica*. https://doi.org/10.1007/s13760-021-01644-y

Gogol, M., Hartmann, H., Wustmann, S., & Simm, A. (2014). Influence of central nervous system-acting drugs on results of cognitive testing in geriatric inpatients. *Zeitschrift für Gerontologie Und Geriatrie*, *47*(4), 279–284. https://doi.org/10.1007/s00391-014-0654-5

Güzel, D., Sağ, S., Sağ, M. S., Tekeoğlu, İ., Kamanlı, A., & Nas, K. (2018). Romatoid artritte bilişsel bozukluğun değerlendirilmesi: eklem yikimi ve hastalik aktivitesinin belirleyici değeri [Evaluation of cognitive impairment in rheumatoid arthritis: predictive value of joint destruction and disease activity]. Kocatepe Tıp Dergisi, 19(3), 86–92. https://doi.org/10.18229/kocatepetip.446832

Gwinnutt, J. M., Toyoda, T., Jeffs, S., Flanagan, E., Chipping, J. R., Dainty, J. R., … MacGregor, A. (2021). Reduced cognitive ability in people with rheumatoid arthritis compared with age-matched healthy controls. *Rheumatology Advances in Practice*, *5*(2), rkab044. https://doi.org/10.1093/rap/rkab044

Hamed, S. A., Selim, Z. I., Elattar, A. M., Elserogy, Y. M., Ahmed, E. A., & Mohamed, H. O. (2012). Assessment of biocorrelates for brain involvement in female patients with rheumatoid arthritis. *Clinical Rheumatology*, *31*(1), 123–132. https://doi.org/10.1007/s10067-011-1795-1

Han, S. D., Buchman, A. S., Arfanakis, K., Fleischman, D. A., & Bennett, D. A. (2013). Functional connectivity networks associated with chronic musculoskeletal pain in old age. *International Journal of Geriatric Psychiatry*, *28*(8), 858–867. https://doi.org/10.1002/gps.3898

Hedges, L., & Olkin, I. (1985). Statistical methods in meta-analysis. In *Stat Med* (Vol. 20). https://doi.org/10.2307/1164953

Hippel, P. T. von. (2015). The heterogeneity statistic I2 can be biased in small meta-analyses. *BMC Medical Research Methodology*, *15*(1), 1–8. https://doi.org/10.1186/s12874-015-0024-z

Karp, J. F., Rudy, T., & Weiner, D. K. (2008). Persistent pain biases item response on the geriatric depression scale (GDS): Preliminary evidence for validity of the GDS-PAIN. *Pain Medicine*, *9*(1), 33–43. https://doi.org/10.1111/j.1526-4637.2007.00406.x

Kim, E. J., & Buschmann, M. T. (2006). Reliability and validity of the faces pain scale with older adults. *International Journal of Nursing Studies*, *43*(4), 447–456. https://doi.org/10.1016/j.ijnurstu.2006.01.001

Kim, S. H., Kim, H., Kim, S., Paek, S., Koh, J. H., Lee, J., … Park, S.-H. (2018). Sleep quality independently affects health-related quality of life and cognitive function in Korean female patients with rheumatoid arthritis: A case-control study. *Journal of Korean Medical Science*, *33*(35), e216. https://doi.org/10.3346/jkms.2018.33.e216

Kotb, H. G., El Attar, R. S., Elabd, H. A., El Nagger, B. M. M. A., & Maabady, M. H. (2019). Cognitive function in rheumatoid arthritis female patients: A prospective cohort study. *Clinical Medicine and Diagnostics*, *9*(2), 36–40. https://doi.org/10.5923/j.cmd.20190902.03

Kunz, M., Mylius, V., Schepelmann, K., & Lautenbacher, S. (2009). Effects of age and mild cognitive impairment on the pain response system. *Gerontology*, *55*(6), 674–682. https://doi.org/10.1159/000235719

Li, J., Chen, J., Qin, Q., Zhao, D., Dong, B., Ren, Q., … Sun, Y. (2018). Chronic pain and its association with obesity among older adults in china. *Archives of Gerontology and Geriatrics*, *76*, 12–18. https://doi.org/10.1016/j.archger.2018.01.009

Liao, X., Mao, C., Wang, Y., Zhang, Q., Cao, D., Seminowicz, D. A., … Yang, X. (2018). Brain gray matter alterations in chinese patients with chronic knee osteoarthritis pain based on voxel-based morphometry. *Medicine*, *97*(12), e0145. https://doi.org/10.1097/MD.0000000000010145

Ma, L., Liu, M., Chen, Z., Chen, X., Yu, S., Chen, Z., & He, H. (2017). Alteration of gray matter texture features over the whole brain in medication-overuse headache using a 3-dimensional texture analysis. *Journal of Headache and Pain*, *18*(1), 112. https://doi.org/10.1186/s10194-017-0820-4

Maneeton, B., Maneeton, N., & Louthrenoo, W. (2010). Cognitive deficit in patients with systemic lupus erythematosus. *Asian Pacific Journal of Allergy and Immunology*, *28*(1), 77. Retrieved from https://www.apjai-journal.org/wp-content/uploads/2017/12/12CognitivedeficitinpatientsVol28No1March2010P77.pdf

McCracken, L. M., & Iverson, G. L. (2001). Predicting complaints of impaired cognitive functioning in patients with chronic pain. *Journal of Pain and Symptom Management*, *21*(5), 392–396. https://doi.org/10.1016/s0885-3924(01)00267-6

McGrath, S., Zhao, X., Steele, R., Thombs, B. D., Benedetti, A., & DEPRESsion Screening Data (DEPRESSD) Collaboration. (2020). Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. *Statistical Methods in Medical Research*, *29*(9), 2520–2537. https://doi.org/10.1177/0962280219889080

Meade, T., Manolios, N., Cumming, S. R., Conaghan, P. G., & Katz, P. (2018). Cognitive impairment in rheumatoid arthritis: A systematic review. *Arthritis Care & Research*, *70*(1), 39–52. https://doi.org/10.1002/acr.23243

Mednieks, J., Naumovs, V., & Skilters, J. (2021). Ideational fluency in patients with rheumatoid arthritis. *Current Rheumatology Reviews*, *17*(2), 205–212. https://doi.org/10.2174/1573397116666201119145640

Merskey, H., & Bogduk, N. (1994). *Classification of chronic pain second edition (revised)*. Seattle: IASP Press.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151*(4), 264–269. https://doi.org/10.1136/bmj.b2535

Moola S, T. C., Munn Z, & P-F., M. (2017.). Chapter 7: Systematic reviews of etiology and risk. In Aromataris E & M. Z (Eds.), *Joanna Briggs Institute reviewer's manual*. The Joanna Briggs Institute. Retrieved from https://reviewersmanual.joannabriggs.org/

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology*, *93*(3), 385–404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Nieuwenhuis-Mark, R. E. (2010). The death knoll for the MMSE: Has it outlived its purpose? *Journal of Geriatric Psychiatry and Neurology*, *23*(3), 151–157. https://doi.org/10.1177/0891988710363714

Ojeda, B., Salazar, A., Dueñas, M., Torres, L. M., Mico, J. A., & Failde, I. (2016). Assessing the construct validity and internal reliability of the screening tool Test Your Memory in patients with chronic pain. *PLoS ONE*, *11*(4). https://doi.org/10.1371/journal.pone.0154240

Oláh, C., Kardos, Z., Andrejkovics, M., Szarka, E., Hodosi, K., Domján, A., … Szekanecz, Z. (2020). Assessment of cognitive function in female rheumatoid arthritis patients: Associations with cerebrovascular pathology, depression and anxiety. *Rheumatology International*, *40*(4), 529–540. https://doi.org/10.1007/s00296-019-04449-8

Oláh, C., Kardos, Z., Sepsi, M., Sas, A., Kostyál, L., Bhattoa, H. P., … others. (2017). Assessment of intracranial vessels in association with carotid atherosclerosis and brain vascular lesions in rheumatoid arthritis. *Arthritis Research & Therapy*, *19*(1), 1–10. https://doi.org/10.1186/s13075-017-1422-x

Oosterman, J. M., Derksen, L. C., Wijck, A. J. M. van, Veldhuijzen, D. S., & Kessels, R. P. C. (2011). Memory functions in chronic pain: Examining contributions of attention and age to test performance. *The Clinical Journal of Pain*, *27*(1), 70–75. https://doi.org/10.1097/AJP.0b013e3181f15cf5

Pamuk, O. N., Kisacik, B., Pamuk, G. E., Onat, A. M., Sayarlioglu, M., Donmez, S., … Keystone, E. C. (2013). Do impaired memory, cognitive dysfunction and distress play a role in methotrexate-related neutropenia in rheumatoid arthritis patients? A comparative study. *Rheumatology International*, *33*(10), 2631–2635. https://doi.org/10.1007/s00296-013-2792-2

Pankowski, D., Wytrychiewicz-Pankowska, K., Janowski, K., & Pisula, E. (2022). Cognitive impairment in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Joint Bone Spine*, *89*(3), 105298. https://doi.org/10.1016/j.jbspin.2021.105298

Petersen, L. E., Baptista, T. S., Molina, J. K., Motta, J. G., Prado, A. do, Piovesan, D. M., … others. (2018). Cognitive impairment in rheumatoid arthritis: Role of lymphocyte subsets, cytokines and neurotrophic factors. *Clinical Rheumatology*, *37*(5), 1171–1181. https://doi.org/10.1007/s10067-018-3990-9

Petersen, L. E., Siara, T., Ribeiro, S. D. S. G., Ilha, M., Grassi-Oliveira, R., Nardi, T. D., … Bauer, M. E. (2015). Premature immunosenescence is associated with memory dysfunction in rheumatoid arthritis. *Neuroimmunomodulation*, *22*(3), 130–137. https://doi.org/10.1159/000358437

Petra, C. V., Visu-Petra, L., Buta, M., Tămaș, M. M., Benga, O., & Rednic, S. (2020). A computerized assessment of verbal and visuospatial memory (dys) functions in patients with rheumatoid arthritis. *Psychology Research and Behavior Management*, *13*, 619. https://doi.org/10.2147/PRBM.S261312

Qu, P., Yu, J., Xia, L., & Chen, G. (2018). Cognitive performance and the alteration of neuroendocrine hormones in chronic tension-type headache. *Pain Practice*, *18*(1), 8–17. https://doi.org/10.1111/papr.12574

Rock, P. L., Roiser, J., Riedel, W. J., & Blackwell, A. (2014). Cognitive impairment in depression: A systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029–2040. https://doi.org/10.1017/S0033291713002535

Rodríguez-Andreu, J., Ibáñez-Bosch, R., Portero-Vázquez, A., Masramon, X., Rejas, J., & Gálvez, R. (2009). Cognitive impairment in patients with fibromyalgia syndrome as assessed by the mini-mental state examination. *BMC Musculoskeletal Disorders*, *10*, 162. https://doi.org/10.1186/1471-2474-10-162

Roebuck-Spencer, T. M., Glen, T., Puente, A. E., Denney, R. L., Ruff, R. M., Hostetter, G., & Bianchini, K. J. (2017). Cognitive screening tests versus comprehensive neuropsychological test batteries: A national academy of neuropsychology education paper†. *Archives of Clinical Neuropsychology*, *32*(4), 491–498. https://doi.org/10.1093/arclin/acx021

Rossetti, H. C., Lacritz, L. H., Cullum, C. M., & Weiner, M. F. (2011). Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology*, *77*(13), 1272–1275. https://doi.org/10.1212/WNL.0b013e318230208a

Ruscheweyh, R., Fritz, A., Eggert, T., Azad, S.-C., & Straube, A. (2018). Oculomotor disturbances in patients with chronic nonspecific spinal pain. *Pain Medicine*, *19*(10), 2031–2038. https://doi.org/10.1093/pm/pnx291

Scherder, E., Oosterman, J., Swaab, D., Herr, K., Ooms, M., Ribbe, M., … Benedetti, F. (2005). Recent developments in pain in dementia. *BMJ (Clinical Research Ed.)*, *330*(15731144), 461–464. https://doi.org/10.1136/bmj.330.7489.461

Schmidt-Wilcke, T., Wood, P., & Lürding, R. (2010). Kognitive defizite bei fibromyalgiepatienten. [Cognitive impairment in patients suffering from fibromyalgia. An underestimated problem.]. *Schmerz (Berlin, Germany)*, *24*(1), 46–53. https://doi.org/10.1007/s00482-009-0872-8

Schofield, P. (2007). Pain in older adults: Epidemiology, impact and barriers to management. *Reviews in Pain*, *1*(1), 12–14. https://doi.org/10.1177/204946370700100104

Segura-Jiménez, V., Álvarez-Gallardo, I. C., Carbonell-Baeza, A., Aparicio, V. A., Ortega, F. B., Casimiro, A. J., & Delgado-Fernández, M. (2015). Fibromyalgia has a larger impact on physical health than on psychological health, yet both are markedly affected: The al-Ándalus project. *Seminars in Arthritis and Rheumatism*, *44*, 563–570. Elsevier. https://doi.org/10.1016/j.semarthrit.2014.09.010

Seo, C. H., Park, C.-H., Jung, M. H., Jang, S., Joo, S. Y., Kang, Y., & Ohn, S. H. (2017). Preliminary investigation of pain-related changes in cerebral blood volume in patients with phantom limb pain. *Archives of Physical Medicine and Rehabilitation*, *98*(11), 2206–2212. https://doi.org/10.1016/j.apmr.2017.03.010

Shehata, G. A., Abdel-Kareem, M., El Adl, A. H. R., & Yassin, A. N. (2010). Subclinical cerebrovascular cognitive function, and mood changes in patients with systemic lupus erythematosus. *Open Access Rheumatology: Research and Reviews*, *2*, 17–25. https://doi.org/10.2147/oarrr.s9711

Stott, J., Scior, K., Mandy, W., & Charlesworth, G. (2017). Dementia screening accuracy is robust to premorbid IQ variation: Evidence from the addenbrooke's cognitive examination-III and the test of premorbid function. *Journal of Alzheimer's Disease*, *57*(4), 1293–1302. https://doi.org/10.3233/JAD-161218

Terassi, M., Ottaviani, A. C., Souza, É. N. de, Fraga, F. J., Montoya, P., Pavarini, S. C. I., & Hortense, P. (2021). Cognition and chronic pain: An analysis on community-dwelling elderly caregivers and non-caregivers. *Arquivos de Neuro-Psiquiatria*, *79*(3), 201–208. https://doi.org/10.1590/0004-282X-ANP-2019-0459

Tiwari, V. K., Nanda, S., Arya, S., Bhatia, R., Kumar, U., Sharma, R., & Kumaran, S. S. (2021). Correlating cognition and cortical excitability with pain in fibromyalgia: A case control study. *Advances in Rheumatology*, *61*(1), 10. https://doi.org/10.1186/s42358-021-00163-x

Tombaugh, T., McDowell, I., Kristjansson, B., & Hubley, A. (1996). Mini-Mental State Examination (MMSE) and the Modified MMSE (3MS): A psychometric comparison and normative data. *Psychological Assessment*, *8*(1), 48. https://doi.org/10.1037/1040-3590.8.1.48

Torkamani, M., Ernst, L., Cheung, L. S., Lambru, G., Matharu, M., & Jahanshahi, M. (2015). The neuropsychology of cluster headache: Cognition, mood, disability, and quality of life of patients with chronic and episodic cluster headache. *Headache: The Journal of Head and Face Pain*, *55*(2), 287–300. https://doi.org/10.1111/head.12486

Veldhuijzen, D. S., Sondaal, S. F. V., & Oosterman, J. M. (2012). Intact cognitive inhibition in patients with fibromyalgia but evidence of declined processing speed. *The Journal of Pain*, *13*(5), 507–515. https://doi.org/10.1016/j.jpain.2012.02.011

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, *36*(3), 1–48. Retrieved from https://doi.org/10.18637/jss.v036.i03

Vitturi, B. K., Nascimento, B. A. C., Alves, B. R., de Campos Sobolewski Carneiro, F., & Torigoe, D. Y. (2019). Cognitive impairment in patients with rheumatoid arthritis. *Journal of Clinical Neuroscience*, *69*, 81–87. http://dx.doi.org/10.1016/j.jocn.2019.08.027

Wang, R., Dong, Z., Chen, X., Liu, R., Zhang, M., Wu, J., & Yu, S. (2014). Cognitive processing of cluster headache patients: Evidence from event-related potentials. *The Journal of Headache and Pain*, *15*. https://doi.org/10.1186/1129-2377-15-66

Wang, Y., Bao, F., Ma, S., Guo, C., Jin, C., Zhang, M., & Li, D. (2014). Thalamic metabolic alterations with cognitive dysfunction in idiopathic trigeminal neuralgia: A multivoxel spectroscopy study. *Neuroradiology*, *56*(8), 685–693. https://doi.org/10.1007/s00234-014-1376-5

Weiner, D. K., Rudy, T. E., Morrow, L., Slaboda, J., & Lieber, S. (2006). The relationship between pain, neuropsychological performance, and physical function in community-dwelling older adults with chronic low back pain. *Pain Medicine*, *7*(1), 60–70. https://doi.org/10.1111/j.1526-4637.2006.00091.x

Xiang, Y., Chen, S., Lin, H., Xiong, W., & Zheng, Z. (2021). Cognitive function and white matter lesions in medication-overuse headache. *Journal of Pain Research*, *14*, 1845–1853. https://doi.org/10.2147/JPR.S310064

Chapter 2: Major Research Project

How is the prediction of dementia using cognitive scores affected by comorbid pain?

Prepared in accordance with the author requirements for the journal Psychological Medicine
https://www.cambridge.org/core/journals/psychological-medicine/information/instructions-contributors

Plain English summary of Major research Project

Title: How is the prediction of dementia using cognitive scores affected by comorbid pain?

Word count: 488 words

Background

When investigating possible dementia clinical staff often use a type of tool called a cognitive screen, which measures cognitive (mental) abilities such as concentration and memory. However we know that factors besides dementia can affect these abilities, including chronic pain (Moriarty, McGuire, and Finn, 2011). It is possible that people experiencing pain are tricky to identify with dementia, or are wrongly assumed to have dementia. This study examined this using the UK Biobank, a large existing dataset of volunteers which contains information on pain, cognitive performance, and any dementia diagnosis.

Aims and questions

Firstly, can the UK Biobank cognitive test scores predict who goes on to get dementia? Then, is that prediction worse for the volunteers who reported chronic pain when they completed the tests?

Methods

Participants: The study used selected participants from the UK Biobank, starting with people who got a dementia diagnosis within four years of visiting the project to do the cognitive tests, which we call our cases. Each case was matched up with three more participants (our controls) who never got a dementia diagnosis and were the same sex and had similar age and education. UK Biobank has updated information about dementia as well as other conditions (like stroke) used to exclude participants. All participants were recruited between 2007-2010 to UK Biobank, and attended their assessment centres where they gave consent (and the project updates the dataset for people who decide to withdraw later).

Design: The study built statistical models to try to identify dementia diagnosis using cognitive information, and see how these are affected by pain. One set of models compared the connection between cognitive score and dementia diagnosis, to see if it is weaker for the volunteers with chronic pain, making it generally less useful. Another looked at whether volunteers with chronic pain were more likely to be sorted into a 'expect to get dementia category,' wrongly. Analyses were also repeated with parts of the data, such as just one type of dementia (like Alzheimer's Disease) or participants younger than 65. All analysis was based on the existing UK Biobank data.

Main findings and conclusions

Our models confirmed that the cognitive information is useful in predicting dementia up to four years in the future - worse scores mean dementia is more likely. This is also true for people with chronic pain. However, using one rule to sort people into categories may end up making more mistakes for dementia-free people when they have chronic pain, leading to 'false alarms' - especially in the younger participants. This suggests that using cognitive screening for dementia is likely to be useful for people with chronic pain, but we may need to look at how they are used and the rules we apply to them.

References

Moriarty, O., McGuire, B. E., and Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in neurobiology*, *93*(3), 385–404.

Abstract

Background. Chronic pain affects cognition, but this is not typically accounted for when using brief cognitive tests to identify dementia. Using a large general population cohort this study sought to understand how classification of dementia using a small set of cognitive measures is affected by the presence of pain.

Methods. The study used data from the UK Biobank dataset, including cognitive measures combined into a single composite score using principal components analysis. Cases were individuals who developed dementia within four years of a project visit. Controls (individuals without dementia) were matched using an algorithm based on demographic variables and project visit considerations. Pain status was determined by self-report. Conditional logistic regression determined whether a composite cognitive score could predict dementia outcome, and receiver-operating characteristic curves were used to determine rates of diagnosis error for each pain status for further regression analyses.

Results. This study included 224 cases with an ultimate dementia diagnosis and 672 matched controls in 1:3 clusters (age at visit 64.97 M, 6.75 SD; 46% women). Cognitive scores predicted dementia status, and their utility was unaffected by pain status (OR = 1.05, 95% CI = 0.771 - 1.429). Being falsely classified as a case was more likely for chronic pain controls, but only in a younger sub-group (OR 1.175, 95% CI 1.037 - 1.33).

Conclusions. For people with chronic pain, brief cognitive information may be predictive of future dementia status, but false positive classification may be elevated when appropriate norm groups are unavailable.

Introduction

Early diagnosis of dementia is crucial to support those affected by the disease. This is commonly prioritised by government policy (e.g. The Scottish Government, 2010), but is not straightforward. NICE guidance recommends the use of cognitive testing as an early component of the diagnostic process (Duff, 2018): instruments commonly used include the Mini-Mental State Examination (MMSE, Folstein, Folstein, and McHugh, 1975), the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) and Addenbrooke's Cognitive Examination-III (ACE-III, Hsieh, Schubert, Hoon, Mioshi, and Hodges, 2013). Cognitive screens generate scores that are appraised relative to benchmarks or thresholds, providing standardisation and simplicity. Ambiguous cases may then be assessed using lengthier test batteries.

The use of cognitive screens does not allow for factors unrelated to organic brain disease that may influence the results. For instance variability in premorbid intelligence appears to affect performance on the MMSE and MoCA (Alves, Simões, Martins, Freitas, and Santana, 2013)[6]. Another such factor is pain, an experience that is increasingly prevalent as people age (Blyth et al., 2001). Pain is also present in some neurological conditions, meaning that "neuropsychologists are likely to have frequent encounters with chronic pain (CP) patients" (Epker and Ogden, 2013, p. p142).

Chronic pain is defined as pain that lasts for more than three months (Carville, Constanti, Kosky, Stannard, and Wilkinson, 2021), and its impact on cognition is

[6] though not the ACE-III, Stott, Scior, Mandy, and Charlesworth (2017).

described in a number of reviews (Berryman et al., 2013; Meade, Manolios, Cumming, Conaghan, and Katz, 2018; Moriarty, McGuire, and Finn, 2011) including the previous chapter. These reviews suggest that individuals suffering from chronic pain experience difficulties with attentional tasks; memory issues including poorer performance on spatial and verbal tasks; slower reaction time on timed cognitive tests; and impaired executive functioning including planning and controlled behaviour. Furthermore scores on screening tests such as the MMSE have been shown to be lower in samples experiencing pain (see e.g. Pankowski, Wytrychiewicz-Pankowska, Janowski, and Pisula, 2022), meaning that pain may bring individual scores below clinical thresholds for dementia, producing false positive diagnoses. As to date this has not been directly investigated, this study does so using an existing dataset, UK Biobank.

UK Biobank contains extensive clinical information that includes reporting of presence of pain at various body locations and whether pain has lasted more than three months, therefore providing an indication of chronic pain. The dataset includes a number of cognitive measures including tests of prospective memory, processing speed, visual memory, and verbal-numerical reasoning. These four measures have been shown to be significant predictors of future dementia diagnosis over and above established risk factors such as hypertension or a family history of dementia up to eight years into the future (Calvin et al., 2019). It seems plausible that these measures would also have some ability to identify dementia over timescales closer to those involved in clinical investigations independent of other risk factors, which constitutes an initial research question (RQ):

1. How effectively do the UK Biobank cognitive measures discriminate future dementia cases from non-cases?

Following this, the study will address two further questions:

2. Does comorbid pain alter the relationship between cognitive testing scores and dementia status, meaning that scoring better or worse provides less insight for diagnosis? If so, to what degree?
3. Does comorbid pain increase the likelihood of an erroneous classification of dementia on the basis of cognitive test scores? If so, to what degree?

Methods

Database / study participants

Launched in 2006, the UK Biobank "is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants" (UK Biobank, 2021a, sec. 1). This prospective cohort study monitors health records for its participants to capture reports of ICD diagnoses including dementia. The UK Biobank resource exists for "bona fide researchers ….to conduct health-related research that is in the public interest" (UK Biobank, 2021b, sec. 2). Researchers apply to access the dataset and those accepted register their programmes of work with the central UK Biobank team. Data is supplied as extracts composed of the relevant variables.

Participants give written informed consent and are free to withdraw their data at any time. All data are anonymised centrally and an individual's data points are identified only by an identity code, with the identity log held centrally by UK Biobank and not shared with researchers. Use of UK Biobank data does not require project-specific ethical approval due to pre-existing approval as a research tissue bank from the NHS National Research Ethics service (reference 21/NW/0157; Appendix B1.1, pp. 119-123). In accordance with the ethics committee conditions, the first author's NHS Research and Development department was notified that this study was being conducted (Appendix B1.2, p. 124).

Visits: All participants attended one of 22 UK Biobank assessment centres for a baseline visit (occurring between 2006-2010) and some (depending on geographic location) were offered opportunities for follow-up visits. For this study the relevant follow-up visits were three where the relevant cognitive assessments were repeated: a first follow-up occurring between 2012-13, a neuroimaging visit (wave commenced 2014) and a second imaging visit commencing 2019. Within this article these will be referred to as visits 1 to 4. The participants were aged between 40 and 69 at the time of visit 1.

Data was filtered to exclude any participant who self-reported any of the following: stroke, neurological cancers, and non-cancer related neurological conditions, as these conditions had the potential to have a large effect on cognition and crowd out the effects of interest. As detailed later, data was then substantially reduced to a set of cases who acquired a dementia diagnoses and their matched controls.

Cognitive measures

The four cognitive measures used in this study were developed by UK Biobank, with all measures except verbal-numerical reasoning designed with reference to validated tests and assessed for validity and reliability. In addition three of the tests (visual memory, prospective memory and verbal-numerical reasoning) correlate with the Mini-ACE dementia assessment (r .27 - .35, Fawns-Ritchie and Deary, 2020). Participants completed these measures on a touchscreen device at each in-person visit to UK Biobank, with no involvement from staff. A summary of the measures is provided in Table 1.

Table 4: *UK Biobank cognitive measures used for predicting dementia diagnosis.*

Test	Description	Scoring
Visual memory	Memorising the position of different symbols shown on cards, which are then shown face-down. Participant must select pairs with matching symbols in as few attempts as possible.	Errors made
Prospective memory	At the end of the cognitive section, participants are presented with instructions but must remember to apply a change to the instructions given to them earlier.	1 if correct response, 0 for mistake
Verbal-numerical reasoning	Multiple-choice problems tapping logical and reasoning ability in verbal and numerical domains.	Score between 0 and 13
Reaction time	Akin to the game "Snap," participants must quickly press a button-box whenever two identical cards are shown on-screen.	Mean time of matches (ms)

Determination of incident dementia

UK Biobank is regularly updated with information from a range of healthcare contexts (e.g. death register, hospital inpatient records), with permissions for these data linking arrangements managed centrally. This allows access to recorded diagnoses based on the ICD10 (International Classification of Diseases, 10th revision, World Health Organization, 2004), including first incidences of dementia namely: Alzheimer's Disease (ICD F00 and G30), vascular dementia (ICD F01) and dementia of another origin (F02, F03, G31). The earliest first incidence of a dementia syndrome determined the date of diagnosis. The type of dementia was specified by the latest incidence of a dementia syndrome[7], allowing for a correction of diagnosis based upon further evidence.

Measurement of pain

A previous study using UK Biobank data (Allen, Gilbody, Atkin, and van der Feltz-Cornelis, 2020) used self-report survey responses to create a dichotomous variable for chronic pain (considered by the ICD as pain continuing for at least 3 months). Participants were asked "In the last month have you experienced any of the following that interfered with your usual activities?" with a list of pain locations e.g. "back pain." This was deemed as chronic if the patient replied affirmatively to a follow-up question "have you had [… pain] for more than 3 months?" with non-affirmative answers denoting that this pain was acute only. Over 215k participants indicated

[7] in most cases this was the same as the first.

some form of chronic pain at baseline assessment. In the current study a variable was computed for each of the four visits per participant that denoted whether they were at that visit experiencing i) no pain - all initial “no”’s ii) acute pain - at least one initial “yes,” no “yes” for any follow-up question, or iii) chronic pain (at least one “yes” to both initial and follow-up questions).

Participant selection and matching

The analysis took a nested case-control design intended to match each case with up to three controls on demographic and study-specific variables. Matching to reduce confounder variable imbalance between groups means that the model subsequently fitted should yield more precise estimates (Gelman, Hill, and Vehtari, 2020).

Eligible case status was determined by dementia status (as determined above) that was chronologically close enough to a prior relevant UK Biobank visit. Vliet et al. (2013) investigated time from onset of dementia symptoms to dementia diagnosis, finding 3.8 years passed between symptom development and diagnosis for a combined group of younger- and older-onset cases. The current study looked at diagnosis which was first recorded up to four years after a relevant UK Biobank visit. The chronologically closest visit before that diagnosis was evaluated: if within four years, this was denoted the ‘active visit’ for that case. Cases who reported only acute pain at their active visit were excluded.

Eligible control status was determined by being dementia-free at the time of analysis, which allowed them to enter a pool for potential matching. From this pool, controls were matched to cases using an optimal matching algorithm conducted with the R *ccoptimalmatch* package (Mamouris and Nassiri, 2021) with the goal of creating clusters of three controls per case. Controls could only be considered for a cluster when they shared with a case: education outcome (degree or no degree at baseline); sex; and available data from the visit corresponding to the case active visit (henceforth the control active visit). In addition there could be a maximum of two years age difference from the case, control pain status for the active visit could not be 'acute' (note however that cases and controls were *not* matched on pain status in any way) and controls must have survived from their active visit for at least as long a period as had elapsed from the one from their matched case's active visit to the date of first dementia diagnosis. Matching then preferentially chose controls with as close an age as possible from available matches using an algorithmic process that preferentially assigned controls with fewer potential matches.

Following matching, measures that were repeated at multiple visits (e.g. age) and derived variables such as cognitive composite (PCA) scores were filtered/selected such that only those for the active visit were carried forward into the final analyses.

Statistical analysis

UK Biobank was extracted and processed in Stata to create the neurological exclusion variable and quality-assessed versions of key cognitive variables. Data was then further processed and analysed using R (version 4.1.2). Analysis code can be found in Appendix B2 (p. 126).

Principal Component Analysis

Following the approach taken by Fawns-Ritchie and Deary (2020) principal component analyses (PCA) were conducted for all available data from the selected cognitive tests at the four available visits (Visit 1 n = 163,706, Visit 2 n =19,967, Visit 3 n =44,715, Visit 4 n =4,215), after firstly transforming those scores with non-normal distributions. In each instance after reviewing eigenvalues and screeplots the first unrotated principal component was saved as a new variable (specific to that visit) denoting overall cognitive performance. The primary factor scores were normally distributed and the decision was made to convert these into z-scores with a higher positive z-score denoting better cognitive performance. Full information is found in Appendix B3, pp. 126-133.

Model construction

This study took a conditional logistic regression approach, using an individual-level matched design. The analysis used a exact conditional likelihood method, with the Breslow method of handling tied data within clusters (advisable for 1:n matching). As controls and cases were matched by age, sex, and education, the analysis did not adjust for these variables.

The initial step (addressing RQ1) involved regression of dementia status (i.e. case or control) upon the general cognitive score. Addressing RQ2 involved introducing further regressors to the model to determine whether cognitive score and pain interact in predicting dementia status. Model results are reported as odds ratio (OR) with 95% confidence interval (CI). This main model was followed by sub-analyses for:

cases with an Alzheimer's Disease diagnosis, those with a Vascular Dementia diagnosis, for those age 65 or greater and for those aged below 65. A sensitivity analysis repeated the main model but included only clusters where the dementia diagnosis date was within 2 (rather than 4) years of the active visit. To address RQ3 the regression model and Receiver-Operating Characteristic curve analysis was used to identify a threshold for the cognitive score that maximises correct identification of dementia. This cut-off then allowed categorisation of the dataset and investigation of diagnostic accuracy for participants with and without chronic pain using regression via the *estimatr* package (Blair, Cooper, Coppock, Humphreys, and Sonnet, 2022), using an ordinary least squares (OLS) approach using the CR (cluster-robust) estimator and computing robust standard errors that account for case-cluster membership.

Results

From the extracted UK Biobank dataset, 9,304 individuals had a dementia diagnosis (age at baseline 63.61 M, 5.47 SD, 46% women, 20% with degree), forming the initial pool of cases. Following the data reduction and matching process described above (and described in Appendix B3 pp. 126-127), cases were reduced to a sample of 224, who had similar characteristics to the full pool (age at baseline 62.79 M, 5.68 SD, age at active visit 64.97 M, 6.75 SD, 39% women, 25% with degree). Table 2 describes the final sample with details summarised by dementia type and chronic pain status. The most frequent diagnosis was of 'other dementia' reflecting uncertainty of diagnosis or mixed dementia aetiology.

Controls were successfully matched in a 3:1 ratio, meaning 672 controls and a total sample of 896. Controls were fully matched for sex and education, and age difference was zero for all but two clusters (in each instance due to one control with a one year difference). Controls were not matched for pain status and Table 2 shows for each row the frequency of clusters with 0,1,2, or 3 chronic-pain experiencing controls. In total, 324 controls reported chronic pain and 348 reported no pain at time of study. 113 cases reported chronic pain and 111 reported no pain at time of study.

Case cognitive performance was poorer than controls (M = -0.918, SD 1.152 vs M= -0.323, SD = 1.034). Differences due to pain were fairly small: for controls, chronic pain M = -0.415 , SD = 1.054 versus pain-free -0.237, SD = 1.008; for cases, chronic pain M = -0.974 , SD 1.136 versus pain-free M = -0.862, SD = 1.171), with Table 2 presenting further information on pain differences in controls.

Model outputs

Conditional logistic regression regressing dementia status on cognitive score found lower scores predicted dementia OR = 0.565 (95% CI = 0.482 - 0.662), answering RQ1 affirmatively. Analysis for RQ2 introduced regressors of (i) pain status as an inter-mediate step and (ii) pain status and an interaction term for cognitive score and pain.

In the three-term model, cognitive score remained associated with dementia, OR = 0.551 (95% CI = 0.442 - 0.687), z = -5.298, $p < .001$. Chronic pain status was not associated with disease outcome, OR = 1.138 (95% CI = 0.771 - 1.681), z = 0.652, p = 0.5141. The interaction term was not associated with disease outcome, OR = 1.05 (95% CI = 0.771 - 1.429), z = 0.308, p = 0.758.

***Table 2**: Sample summary information*

Group	Full dataset			AD		VaD		Other		Older		Younger	
Pain status	combined	F	CP	F	CP	F	CP	F	CP	F	CP	F	CP
no of clusters (k)	224	111	113	28	22	11	17	72	74	74	62	37	51
Female k (%)	87 (39)	40 (36)	47 (42)	12 (43)	14 (64)	1 (9)	5 (29)	27 (38)	28 (38)	27 (36)	27 (44)	13 (35)	20 (39)
Degree-holder k (%)	57 (25)	33 (30)	24 (21)	7 (25)	3 (14)	4 (36)	3 (18)	22 (31)	18 (24)	22 (30)	14 (23)	11 (30)	10 (20)
Age M (SD) at active visit	64.97 (6.75)	65.53 (6.4)	64.42 (7.06)	65.93 (4.88)	66 (4.9)	65.27 (4.92)	66.94 (4.35)	65.42 (7.13)	63.36 (7.88)	69.05 (3.48)	69.31 (3.36)	58.49 (4.9)	58.47 (5.67)
Cognitive z-score mean (SD)	-0.92 (1.15)	-0.86 (1.17)	-0.97 (1.14)	-1.58 (0.99)	-1.59 (1.07)	-0.84 (1.15)	-1.17 (0.97)	-0.58 (1.13)	-0.74 (1.13)	-1.05 (1.14)	-1.14 (0.97)	-0.49 (1.16)	-0.78 (1.3)
k with n=0/1/2/3 pain controls	30/86/86/22	18/43/41/9	12/43/45/13	3/11/10/4	0/4/11/7	1/5/5/0	0/4/12/1	14/27/26/5	12/35/22/5	12/29/28/5	3/25/28/6	6/14/13/4	9/18/17/7
Difference in control cognition score by pain status	CP poorer, p = 0.024			CP poorer, p = 0.028		no sig. difference		no sig. difference		no sig. difference		CP poorer, p = 0.008	

F = free of pain, CP = chronic pain, AD = Alzheimer's Disease, VaD = Vascular Dementia, Other = Other/mixed dementia, Older = aged 65 or older, Younger = below 65 years. Differences in control cognitive scores analysed using T-test.

Table 3 depicts these results alongside those for a sensitivity analysis conducted with clusters whose case was diagnosed within two years of the active visit (rather than four)[8]. It also presents sub-analyses for dementia subtypes and age-based subgroups. These results all involve a statistically significant cognitive coefficient with non-significant coefficients for pain status and the interaction term. Due to this the investigation of coefficients for chronic pain and pain-free groups was not attempted.

False positive rates

A Receiver Operating Characteristic analysis using cognitive score to predict diagnostic status returned an optimal cutpoint of -0.593 to classify the data, using a method that maximised the Youden metric (obtained 0.246). The area under the curve (AUC) was 0.652 (95% CI 0.609 - 0.698), with accuracy 0.633 (95% CI 0.472 - 0.705), sensitivity 0.603 (95% CI 0.32 - 0.819) and specificity 0.643 (95% CI 0.374 - 0.848).

This cutpoint was used to give participants a positive or negative dementia designation, with RQ3 focusing on false positive designations for people with chronic

[8] A sensitivity analysis was considered using another operationalisation of pain (based on pain condition first occurrence diagnosis codes) but the resulting categorisation was at odds with self-reported pain and not conducted (details in Appendix B3 p. 132).

pain. As Figure 1a shows, a higher proportion of participants with chronic pain acquire a false positive designation, $\chi(896,1) = 5.675$, p = 0.017.

However, as pain groups are not matched on other variables, we conducted logistic regressions using OLS on controls, regressing positive/negative classification on age, education, sex and pain status. The OR for pain status was 1.072, the 95% CI just including 1 (0.991 - 1.161).

Due to larger cognitive score differences by pain status in younger controls (under 65, see Table 2), this subgroup was subjected to a similar analysis using the same cut-point. Figure 1b shows the proportion of younger controls who fall below this cut-point, with OR due to having chronic pain of 1.175 (95% CI 1.037 - 1.33). A re-analysis using a cut-point based on data from the younger-group found a smaller and non-significant greater OR for chronic pain. Model outputs for these analyses are found in Table 4.

Exploratory analyses

As cognitive score differences between chronic pain and pain-free controls appeared small (Table 1) this was systematically investigated using the same robust methods (controlling for matching variables and denoting clusters), finding an overall non-significant difference of -0.123 (95% CI -0.284 - 0.039), p = 0.136. Given this, further analyses explored the degree of difference for each of the individual cognitive tests described in Table 1. Scores only differed by pain status for the reasoning task (estimated difference = 0.415, 95% CI = 0.105 - 0.725, p = 0.009 and marginally for the prospective memory task (estimated difference = 0.069, 95% CI = 0 - 0.138, p = 0.051).

***Table 5**: Conditional logistic regression information.*

Sample	No. of clusters k (participants n)	Term	OR (95% CI)	z	p-value
Overall	224	Cognitive score (z)	**0.551 (0.442-0.687)**	**-5.298**	**< 0.001**
	(896)	Chronic pain status	1.138 (0.771-1.681)	0.652	0.514
		Cognitive score interaction with pain	1.05 (0.771-1.429)	0.308	0.758
Diagnosis =< 2 years	81	Cognitive score (z)	**0.54 (0.368-0.792)**	**-3.150**	**0.002**
	(324)	Chronic pain status	1.154 (0.596-2.233)	0.424	0.672
		Cognitive score interaction with pain	0.999 (0.601-1.662)	-0.003	0.997
AD	50	Cognitive score (z)	**0.235 (0.116-0.474)**	**-4.047**	**< 0.001**
	(200)	Chronic pain status	0.739 (0.207-2.632)	-0.467	0.641
		Cognitive score interaction with pain	1.6 (0.685-3.74)	1.085	0.278
VaD	28	Cognitive score (z)	0.744 (0.386-1.435)	-0.881	0.378
	(112)	Chronic pain status	0.947 (0.299-3)	-0.093	0.926
		Cognitive score interaction with pain	0.712 (0.308-1.644)	-0.796	0.426
Age 65 +	136	Cognitive score (z)	**0.554 (0.421-0.73)**	**-4.203**	**< 0.001**
	(544)	Chronic pain status	0.881 (0.512-1.516)	-0.458	0.647
		Cognitive score interaction with pain	0.959 (0.639-1.44)	-0.201	0.84
Age under 65	88	Cognitive score (z)	**0.581 (0.399-0.847)**	**-2.823**	**0.005**
	(352)	Chronic pain status	1.524 (0.868-2.675)	1.467	0.142
		Cognitive score interaction with pain	1.069 (0.65-1.757)	0.261	0.794

Bolded sections depict significant terms. OR = Odds ratio, AD = Alzheimer's Disease, VaD = Vascular Dementia.

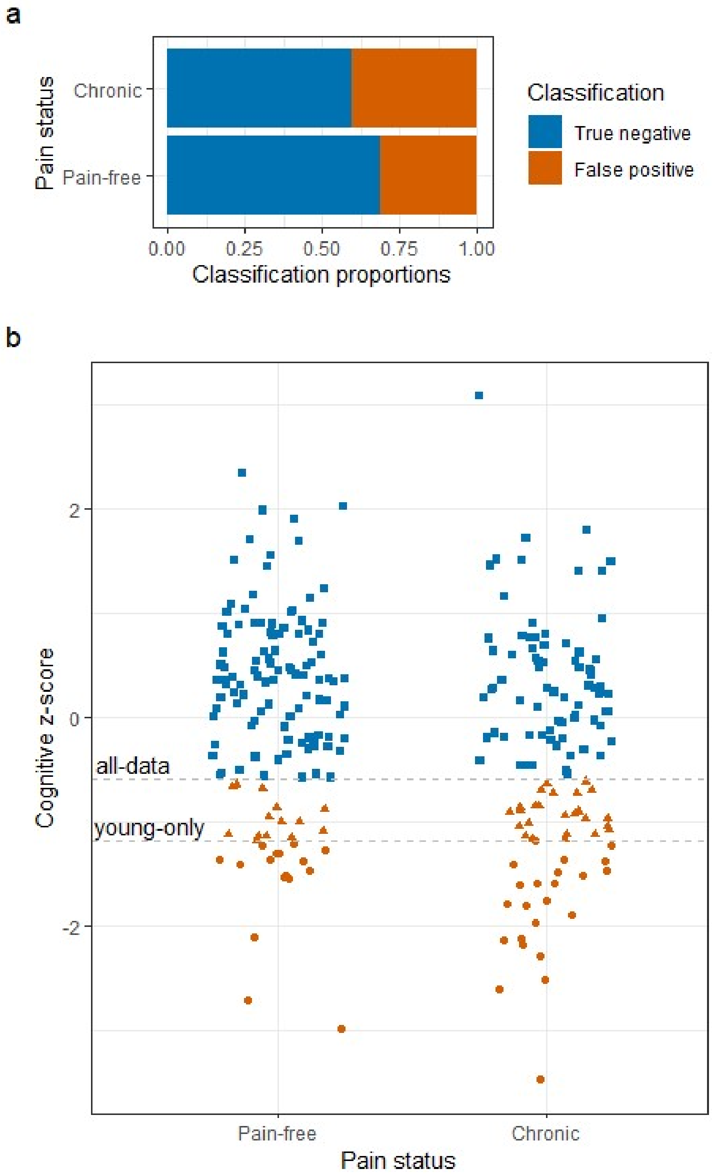


Figure 1. Panel a) denotes proportions of false positive classifications in all-dataset controls with and without chronic pain. Panel b) denotes pattern of cognitive score in controls under the age of 65, against two cut-points. Blue points are always correctly classified, red points false positively classified against the cut-point based on all data, circles remain false positively classified when using the cut-point based only on under-65 data.

Continuing this exploratory approach, a composite PCA score was derived from just these two measures; when substituted in the robust logistic regressions concerning false positive classifications, larger effects were found for the younger subgroup and the overall dataset (where the CI no longer included 1); these are included in Table 4.

When substituted in the conditional logistic regression models, it produced a similar pattern of findings to those shown in Table 3 with no significant interaction but a significant odds ratio for cognitive score 0.563, 95% CI = 0.453 - 0.698), which was in fact more predictive of dementia status than a score based on the other two variables (reaction time and visual memory: OR 0.701, 95% CI = 0.567 - 0.867).

Discussion

This study investigated the impact of chronic pain upon the diagnostic accuracy of cognitive information to correctly classify individuals as going on to receive a dementia diagnosis. The cognitive measure had utility in predicting dementia status which was not significantly different for people with chronic pain. An analysis of false positive rates found that controls reporting chronic pain were more likely to be classified as belonging to the case group (i.e a false-positive classification) but after the appropriate controls this only remained true for the subgroup (age below 65) with the highest pain-related difference in cognitive scores.

Table 6: *Regression upon false positive classification in controls.*

Analysis type	Regression term	OR (95% CI)	z	p-value	df
Main analysis	Per year of age	**1.01 (1.004 - 1.016)**	**3.407**	**0.001**	**56.638**
	Being male	0.953 (0.879 - 1.033)	-1.176	0.241	176.652
	Possessing degree	**0.852 (0.783 - 0.927)**	**-3.782**	**< 0.001**	**93.244**
	Chronic pain	1.072 (0.991 - 1.161)	1.746	0.082	214.116
Younger group (<65)	Per year of age	**1.015 (1.002 - 1.028)**	**2.451**	**0.023**	**21.942**
	Being male	0.989 (0.872 - 1.121)	-0.183	0.856	60.531
	Possessing degree	0.957 (0.836 - 1.096)	-0.657	0.516	29.577
	Chronic pain	**1.175 (1.037 - 1.33)**	**2.573**	**0.012**	**82.849**
Younger group, cut-point using younger group data only	Per year of age	1.006 (0.996 - 1.015)	1.230	0.232	21.942
	Being male	1.013 (0.919 - 1.117)	0.264	0.793	60.531
	Possessing degree	0.955 (0.855 - 1.067)	-0.844	0.406	29.577
	Chronic pain	1.067 (0.974 - 1.169)	1.413	0.161	82.849
Exploratory: Prospective/ reasoning score only	Per year of age	**1.009 (1.003 - 1.014)**	**3.146**	**0.003**	**56.638**
	Being male	0.98 (0.904 - 1.063)	-0.483	0.63	176.652
	Possessing degree	**0.855 (0.787 - 0.929)**	**-3.750**	**< 0.001**	**93.244**
	Chronic pain	**1.1 (1.02 - 1.187)**	**2.479**	**0.014**	**214.116**
Exploratory: Prospective/ reasoning score only, younger group	Per year of age	1.011 (1 - 1.023)	2.003	0.058	21.942
	Being male	0.98 (0.862 - 1.113)	-0.324	0.747	60.531
	Possessing degree	0.901 (0.788 - 1.031)	-1.587	0.123	29.577
	Chronic pain	**1.181 (1.049 - 1.33)**	**2.800**	**0.006**	**82.849**

Bolded sections depict significant terms. OR = odds ratio.

Comparison with previous research

Calvin et al. (2019) used UK Biobank data to construct models predicting dementia diagnoses eight years from assessment visits. This was a population cohort design (n = 397,485) using a modelling approach that incorporated family history, APOE ε4 genetic information, and used demographics such as age as covariates. The current study finds predictive utility using a smaller matched design and using a single composite cognitive score in the absence of other predictors, to better reflect the use of cognitive screens in clinical practice. In Calvin et al. (2019) cognitive information raised the AUC from .78 to .83, whereas ours (all told) was 0.65.

The (uncontrolled) pain-related differences in cognitive scores in this study (0.179 *z* in controls, 0.112 *z* in dementia cases) are smaller than those reported in the meta-analysis in the last chapter, where estimates of pooled Standardised Mean Difference are closer to 0.7. This could reflect differences in sample characteristics: UK Biobank is known to comprise individuals who are on average healthier and more socioeconomically advantaged than others (Fry et al., 2017), and individuals experiencing more disabling forms of chronic pain may not have participated. The high rates of chronic pain reporting suggest that this may not fully reflect clinical samples. In addition, the matched sample had a mean age of 65 at testing. The previous chapter suggested that older samples saw smaller cognitive score decrements in chronic pain groups - 0.2 (Karp, Rudy, and Weiner, 2008) and .36 (Terassi et al., 2021); limiting our dataset to the under-65s found chronic pain associated with larger cognitive decrements and led controls to be more often false-positively classified with dementia status.

It is also possible that the pain-related cognitive differences seen in the literature sometimes reflect a decline into subsequent dementia - that is, the pain groups reported in this literature do not simply map onto the current studies pain-experiencing controls, but onto the eventual cases (at higher rates than for pain-free participants). If so, this study may provide a more accurate estimate of the impact of pain on cognitive performance relatively unconfounded from associated dementia risk-factors and suggests these are smaller than typically reported. Reviews on the relationship between pain and cognitive decline into dementia are equivocal, with Aguiar et al. (2020) finding no relationship between persistent pain and incident dementia in older adults at followup between 2.75 and 11.8 years, but Innes and Sambamoorthi (2020) found some relationship between chronic pain and adverse cognitive outcomes, albeit with a large amount of heterogeneity.

Differences may also reflect the nature of the cognitive measure used. In unplanned analyses, only two cognitive subtests showed different performance due to pain status. These can be understood in terms of the chronic pain literature, where executive function and working memory deficits are well understood, with prospective memory tapping the former and the reasoning (a timed test comprising logical, numeric and verbal problems) tapping both. A measure based on these subtests continued to be predictive of dementia status and showed a more pronounced higher odds of false positive classification for controls with chronic pain.

This aligns with the previous chapter where the MoCA, with executive function components, yielded higher pain-related differences than the MMSE which does not.

Strengths and Limitations

In considering the applicability of this study to clinical contexts, while the cognitive measures used do address cognitive domains considered in dementia assessment (and several correlate with standard neuropsychological measures including with the Mini-ACE[9], these correlations are fairly modest. In addition, the measures have fairly low test-retest reliability (see Lyall et al., 2016). As such, these cognitive measures should not be considered an equivalent for a standardised cognitive screen such as the MMSE or MoCA, but providing more insight more generally into how brief cognitive information can contribute to dementia detection in the presence of chronic pain.

The study followed Allen, Gilbody, Atkin, and van der Feltz-Cornelis (2020) in using a self-report measure to denote pain status, rather determining using a diagnosis of a chronic pain condition (see Appendix B3 p. 132 for further discussion), which may be another way the study differs from those typical in the literature.

The identification of dementia within this study relies on health record information which is not wholly reliable (Manuel, Rosella, and Stukel, 2010), and under-detection of dementia could lead to more conservative odds ratios being produced. In addition

[9] with the exception of the Reaction Time measure.

definitive classification of dementia type is hampered by being reconstructed from records.

The difficulties faced by people living with dementia in reporting pain are well-documented (see Scherder et al., 2005 for a review) and systematic under-reporting of pain by cases would introduce greater error into the estimates. However, none of the sample had received a dementia diagnosis at the time of data collection, and research on the effect of Mild Cognitive Impairment (Kunz, Mylius, Schepelmann, and Lautenbacher, 2009) and of subtle decrements in cognitive ability (Docking et al., 2014) finds no notable effects on pain responding.

This study did not investigate within-individual changes in cognitive score over time, and future research may wish to investigate whether the course of cognitive decline in the lead-up to dementia diagnosis is similar or different for people with chronic pain.

Conclusion

These analyses suggest that a cognitive score-based indicator of future dementia status up to four years into the future remains informative for a sample with chronic pain, providing no indication that this approach ceases to become discriminative for such populations. The research however raises issues about how to treat scores, especially in a younger subgroup where disparities in cognitive performance were most evident (and more akin to those seen in the literature). Higher rates of false positive diagnosis were observed when using a diagnostic cut-off based on the total dataset, but not when the cut-off was based on available data from that age group.

Ideally, reference groups for evaluating scores should closely resemble the individual investigated, such as groups with chronic pain, but even if this is not available, it is likely to be important to utilise norms based on age.

As suggested by the exploratory analyses, some cognitive measures were more influenced by chronic pain than others, and in these cases false positive classification rose. Other measures were more impervious to the influence of pain, but were less informative in predicting dementia status. This suggests an evaluation of current cognitive screens to see how robust their subdomains are to chronic pain is required and that the feasibility of designing tests that minimise dependency on these while maintaining test accuracy should be explored.

Declaration of interest

None.

References

Aguiar, G. P. C. G. de, Saraiva, M. D., Khazaal, E. J. B., Andrade, D. C. de, Jacob-Filho, W., & Suemoto, C. K. (2020). Persistent pain and cognitive decline in older adults: A systematic review and meta-analysis from longitudinal studies. *Pain*, *161*(10), 2236–2247. https://doi.org/10.1097/j.pain.0000000000001932

Allen, S. F., Gilbody, S., Atkin, K., & van der Feltz-Cornelis, C. (2020). The associations between loneliness, social exclusion and pain in the general population: A n= 502,528 cross-sectional UK Biobank study. *Journal of Psychiatric Research*, *130*, 68–74. https://doi.org/10.1016/j.jpsychires.2020.06.028

Alves, L., Simões, M. R., Martins, C., Freitas, S., & Santana, I. (2013). Premorbid IQ influence on screening tests' scores in healthy patients and patients with cognitive impairment. *Journal of Geriatric Psychiatry and Neurology*, *26*(2), 117–126. https://doi.org/10.1177/0891988713484194

Berryman, C., Stanton, T. R., Bowering, K. J., Tabor, A., McFarlane, A., & Moseley, G. L. (2013). Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain*, *154*(8), 1181–1196. https://doi.org/10.1016/j.pain.2013.03.002

Blair, G., Cooper, J., Coppock, A., Humphreys, M., & Sonnet, L. (2022). *Estimatr: Fast estimators for design-based inference*. Retrieved from https://declaredesign.org/r/estimatr/, https://github.com/DeclareDesign/estimatr

Blyth, F. M., March, L. M., Brnabic, A. J., Jorm, L. R., Williamson, M., & Cousins, M. J. (2001). Chronic pain in Australia: A prevalence study. *Pain*, *89*(2-3), 127–134. https://doi.org/10.1016/s0304-3959(00)00355-9

Calvin, C. M., Wilkinson, T., Starr, J. M., Sudlow, C., Hagenaars, S. P., Harris, S. E., … Gale, C. R. (2019). Predicting incident dementia 3-8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. *Alzheimer's & Dementia*, *15*(12), 1546–1557. https://doi.org/10.1016/j.jalz.2019.07.014

Carville, S., Constanti, M., Kosky, N., Stannard, C., & Wilkinson, C. (2021). Chronic pain (primary and secondary) in over 16s: Summary of NICE guidance. *Bmj*, *373*. https://doi.org/10.1136/bmj.n895

Docking, R. E., Fleming, J., Brayne, C., Zhao, J., Macfarlane, G. J., & Jones, G. T. (2014). Pain reporting in older adults: The influence of cognitive impairment - results from the Cambridge City >75 cohort study. *British Journal of Pain*, *8*(3), 119–124. https://doi.org/10.1177/2049463714527437

Duff, C. (2018). *Dementia: Assessment, management and support for people living with dementia and their carers (NICE guideline 97).* National Institute of Clinical Excellence. Retrieved from National Institute of Clinical Excellence website: https://www.nice.org.uk/guidance/ng97

Epker, J., & Ogden, M. (2013). *The impact of pain and pain-related factors on cognitive functioning* (P. A. Arnett, Ed.). In (pp. 142–165). New York, NY: Oxford University Press.

Fawns-Ritchie, C., & Deary, I. J. (2020). Reliability and validity of the UK Biobank cognitive tests. *PloS One*, *15*(4), e0231627. https://doi.org/10.1371/journal.pone.0231627

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). “Mini-mental state”: A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*(3), 189–198. https://doi.org/10.1016/0022-3956(75)90026-6

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., … Allen, N. E. (2017). Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *American Journal of Epidemiology*, *186*(9), 1026–1034. https://doi.org/10.1093/aje/kwx246

Gelman, A., Hill, J., & Vehtari, A. (2020). *Regression and other stories*. Cambridge University Press.

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *36*(3-4), 242–250. https://doi.org/10.1159/000351671

Innes, K. E., & Sambamoorthi, U. (2020). The potential contribution of chronic pain and common chronic pain conditions to subsequent cognitive decline, new onset cognitive impairment, and incident dementia: A systematic review and conceptual model for future research. *Journal of Alzheimer's Disease*, *78*(3), 1177–1195. https://doi.org/10.3233/JAD-200960

Karp, J. F., Rudy, T., & Weiner, D. K. (2008). Persistent pain biases item response on the geriatric depression scale (GDS): Preliminary evidence for validity of the GDS-PAIN. *Pain Medicine*, *9*(1), 33–43. https://doi.org/10.1111/j.1526-4637.2007.00406.x

Kunz, M., Mylius, V., Schepelmann, K., & Lautenbacher, S. (2009). Effects of age and mild cognitive impairment on the pain response system. *Gerontology*, *55*(6), 674–682. https://doi.org/10.1159/000235719

Lyall, D. M., Cullen, B., Allerhand, M., Smith, D. J., Mackay, D., Evans, J., … others. (2016). Cognitive test scores in UK Biobank: Data reduction in 480,416 participants and longitudinal stability in 20,346 participants. *PloS One*, *11*(4), e0154222. https://doi.org/10.1371/journal.pone.0154222

Mamouris, P., & Nassiri, V. (2021). *Ccoptimalmatch: Implementation of case-control optimal matching*. Retrieved from https://CRAN.R-project.org/package=ccoptimalmatch

Manuel, D. G., Rosella, L. C., & Stukel, T. A. (2010). Importance of accurately identifying disease in studies using electronic health records. *British Medical Journal*, *341*. https://doi.org/10.1136/bmj.c4226

Meade, T., Manolios, N., Cumming, S. R., Conaghan, P. G., & Katz, P. (2018). Cognitive impairment in rheumatoid arthritis: A systematic review. *Arthritis Care & Research*, *70*(1), 39–52. https://doi.org/10.1002/acr.23243

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology*, *93*(3), 385–404. https://doi.org/10.1016/j.pneurobio.2011.01.002

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Pankowski, D., Wytrychiewicz-Pankowska, K., Janowski, K., & Pisula, E. (2022). Cognitive impairment in patients with rheumatoid arthritis: A systematic review and meta-analysis. *Joint Bone Spine*, *89*(3), 105298. https://doi.org/10.1016/j.jbspin.2021.105298

Scherder, E., Oosterman, J., Swaab, D., Herr, K., Ooms, M., Ribbe, M., … Benedetti, F. (2005). Recent developments in pain in dementia. *BMJ (Clinical Research Ed.)*, *330*(15731144), 461–464. https://doi.org/10.1136/bmj.330.7489.461

Stott, J., Scior, K., Mandy, W., & Charlesworth, G. (2017). Dementia screening accuracy is robust to premorbid IQ variation: Evidence from the Addenbrooke's Cognitive Examination-III and the test of premorbid function. *Journal of Alzheimer's Disease*, *57*(4), 1293–1302. https://doi.org/10.3233/JAD-161218

Terassi, M., Ottaviani, A. C., Souza, É. N. de, Fraga, F. J., Montoya, P., Pavarini, S. C. I., & Hortense, P. (2021). Cognition and chronic pain: An analysis on community-dwelling elderly caregivers and non-caregivers. *Arquivos de Neuro-Psiquiatria*, *79*(3), 201–208. https://doi.org/10.1590/0004-282X-ANP-2019-0459

The Scottish Government. (2010). *Scotland's National Dementia Strategy 2010-2013*. The Scottish Government. Retrieved from The Scottish Government website: http://www.wdhscp.org.uk/media/1270/dementia-strategy-2010.pdf

UK Biobank. (2021a). *UK Biobank: About us*. Retrieved from https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us

UK Biobank. (2021b). *UK Biobank: Register*. Retrieved from https://www.ukbiobank.ac.uk/enable-your-research/register

Vliet, D. V., Vugt, M. D., Bakker, C., Pijnenburg, Y., Vernooij-Dassen, M., Koopmans, R., & Verhey, F. (2013). Time to diagnosis in young-onset dementia as compared with late-onset dementia. *Psychological Medicine*, *43*(2), 423–432. https://doi.org/10.1017/S0033291712001122

World Health Organization. (2004). *ICD-10 : International statistical classification of diseases and related health problems : Tenth revision, 2nd ed.* Retrieved from https://apps.who.int/iris/handle/10665/42980

Appendices

Appendix A1 Search strategies

Embase via Ovid

1 ("Addenbrook* Cognit* Exam*" or Mini-ACE or "Abbreviat* Mental Test" or "Montreal Cognit* Assess*" or "Mini Mental State Exam*" or "6-item cognit* impair* test" or "Hopkins Verbal Learning Test" or "Test for the early detection of dementia" or "Test your memory test").tw.
2 (ACE-3 or ACE-R or M-ACE or AMT or ACE-III or MoCA or MMSE or 6CIT or HVLT or TE4D-Cog or TYM).tw.
3 1 or 2
4 exp pain/
5 ((chronic adj5 pain) or fibromyalgia or arthriti* or rheumat* or (chronic adj5 (headache or migraine)) or "neuropathic pain").tw.
6 ("constant-murley score" or "Short form of McGill Pain Questionnaire" or "Pain intensity Visual analogue scale for SF-MPQ" or "Present Pain Intensity scale for SF-MPQ" or "Revised Fibromyalgia Impact Questionnaire" or "McGill Pain Questionnaire" or "Wong-Baker FACES Pain Scale" or "Neck Pain and Disability Scale" or "Color Analog Scale" or "Mankoski Pain Scale" or "Brief Pain Inventory" or "Descriptor Differential Scale of Pain Intensity" or "Oswestry Disability Index" or "Numeric Rating Scale" or "Alder Hey Triage Pain Score" or "Behavioral Pain Scale" or "Critical-Care Pain Observation Tool" or "Dallas Pain Questionnaire" or "Dolorimeter Pain Index" or "Global Pain Scale" or "Lequesne algofunctional index" or "Multiple Pain Rating Scales" or "Numerical 11 point box" or "Roland-Morris Back Pain Questionnaire" or "Wharton Impairment and Pain Scale").tw.
7 4 or 5 or 6
8 (((systematic or state-of-the-art or scoping or literature or umbrella) adj (review* or overview* or assessment*)) or "review* of reviews" or meta-analy* or metaanaly* or ((systematic or evidence) adj1 assess*) or "research evidence" or metasynthe* or meta-synthe*).tw. or systematic review/ or "systematic review (topic)"/ or meta analysis/ or "meta analysis (topic)"/
9 3 and 7
10 9 not 8
11 exp aged/ or exp adult/ or exp middle aged/ or community dwelling person/
12 (adult or elder* or middle-aged or old* or aged or aging).tw.
13 11 or 12
14 10 and 13

Medline via EBSCOhost

S1 (MH "Pain+")

S2 (TI(chronic near/5 pain OR fibromyalgi* OR arthriti* OR rheumat* OR chronic near/5 (headache OR migraine) OR "neuropathic pain")) OR (AB(chronic near/5 pain OR fibromyalgi* OR arthriti* OR rheumat*OR chronic near/5 (headache OR migraine) OR "neuropathic pain"))

S3 (TI("constant-murley score" OR "Short form of McGill Pain Questionnaire" OR "Pain intensity Visual analogue scale for SF-MPQ" OR "Present Pain Intensity scale for SF-MPQ" OR "Revised Fibromyalgia Impact Questionnaire" OR "McGill Pain Questionnaire" OR "Wong-Baker FACES Pain Scale" OR "Neck Pain and Disability Scale" OR "Color Analog Scale" OR "Mankoski Pain Scale" OR "Brief Pain Inventory" OR "Descriptor Differential Scale of Pain Intensity" OR "Oswestry Disability Index" OR "Numeric Rating Scale" OR "Alder Hey Triage Pain Score" OR "Behavioral Pain Scale" OR "Critical-Care Pain Observation Tool" OR "Dallas Pain Questionnaire" OR "Dolorimeter Pain Index" OR "Global Pain Scale" OR "Lequesne algofunctional index" OR "Multiple Pain Rating Scales" OR "Numerical 11 point box" OR "Roland-Morris Back Pain Questionnaire" OR "Wharton Impairment and Pain Scale")) OR (AB("constant-murley score" OR "Short form of McGill Pain Questionnaire" OR "Pain intensity Visual analogue scale for SF-MPQ" OR "Present Pain Intensity scale for SF-MPQ" OR "Revised Fibromyalgia Impact Questionnaire" OR "McGill Pain Questionnaire" OR "Wong-Baker FACES Pain Scale" OR "Neck Pain and Disability Scale" OR "Color Analog Scale" OR "Mankoski Pain Scale" OR "Brief Pain Inventory" OR "Descriptor Differential Scale of Pain Intensity" OR "Oswestry Disability Index" OR "Numeric Rating Scale" OR "Alder Hey Triage Pain Score" OR "Behavioral Pain Scale" OR "Critical-Care Pain Observation Tool" OR "Dallas Pain Questionnaire" OR "Dolorimeter Pain Index" OR "Global Pain Scale" OR "Lequesne algofunctional index" OR "Multiple Pain Rating Scales" OR "Numerical 11 point box" OR "Roland-Morris Back Pain Questionnaire" OR "Wharton Impairment and Pain Scale"))

S4 S1 OR S2 OR S3

S5 (TI("Addenbrooke's Cognitive Examination" OR Mini-ACE OR "Abbreviated Mental Test" OR "Montreal Cognitive Assessment" OR "Mini Mental State Examination" OR "6-item cognitive impairment test" OR "Hopkins Verbal Learning Test" OR "Test for the early detection of dementia" OR "Test your memory test")) OR (AB("Addenbrooke's Cognitive Examination" OR Mini-ACE OR "Abbreviated Mental Test" OR "Montreal Cognitive Assessment" OR "Mini Mental State Examination" OR "6-item cognitive impairment test" OR "Hopkins Verbal Learning Test" OR "Test for the early detection of dementia" OR "Test your memory test"))

S6 TI(ACE-3 OR ACE-R OR M-ACE OR AMT OR ACE-III OR MoCA OR MMSE OR 6CIT OR HVLT OR TE4D-Cog OR TYM) OR AB(ACE-3 OR ACE-R OR M-ACE OR AMT OR ACE-III OR MoCA OR MMSE OR 6CIT OR HVLT OR TE4D-Cog OR TYM)

S7 S5 OR S6

S8 S4 AND S7

S9 (MH "Adult+")

S10 TI ((adult or elder* or middle-aged or old* or aged or aging)) OR AB ((adult or elder* or middle-aged or old* or aged or aging))

S11 S9 OR S10

S12 S8 AND S11

S13 TI (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR AB (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR KW (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR MH ("Review Literature as Topic" OR "Review" OR "Meta-Analysis as Topic" OR "Meta-Analysis" OR "systematic review")

S14 S12 NOT S13

PsycInfo (via EBSCOhost)

S1 TM("Addenbrooke's Cognitive Examination" OR Mini-ACE OR "Abbreviated Mental Test" OR "Montreal Cognitive Assessment" OR "Mini Mental State Examination" OR "6-item cognitive impairment test" OR "Hopkins Verbal Learning Test" OR "Test for the early detection of dementia" OR "Test your memory test")

S2 TI("Addenbrooke's Cognitive Examination" OR Mini-ACE OR "Abbreviated Mental Test" OR "Montreal Cognitive Assessment" OR "Mini Mental State Examination" OR "6-item cognitive impairment test" OR "Hopkins Verbal Learning Test" OR "Test for the early detection of dementia" OR "Test your memory test")

S3 AB("Addenbrooke's Cognitive Examination" OR Mini-ACE OR "Abbreviated Mental Test" OR "Montreal Cognitive Assessment" OR "Mini Mental State Examination" OR "6-item cognitive impairment test" OR "Hopkins Verbal Learning Test" OR "Test for the early detection of dementia" OR "Test your memory test")

S4 TM(ACE-3 OR ACE-R OR M-ACE OR AMT OR ACE-III OR MoCA OR MMSE OR 6CIT OR HVLT OR TE4D-Cog OR TYM)

S5 TI(ACE-3 OR ACE-R OR M-ACE OR AMT OR ACE-III OR MoCA OR MMSE OR 6CIT OR HVLT OR TE4D-Cog OR TYM)

S6 AB(ACE-3 OR ACE-R OR M-ACE OR AMT OR ACE-III OR MoCA OR MMSE OR 6CIT OR HVLT OR TE4D-Cog OR TYM)

S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6

S8 DE("Pain" OR "Acute Pain" OR "Aphagia" OR "Back Pain" OR "Chronic Pain" OR "Headache" OR "Myofascial Pain" OR "Neuralgia" OR "Neuropathic Pain" OR "Somatoform Pain Disorder")

S9 TI(chronic N5 pain OR fibromyalgia OR chronic N5 (headache OR migraine) OR "neuropathic pain")

S10 AB(chronic N5 pain OR fibromyalgia OR chronic N5 (headache OR migraine) OR "neuropathic pain")

S11 TI("constant-murley score" OR "Short form of McGill Pain Questionnaire" OR "Pain intensity Visual analogue scale for SF-MPQ" OR "Present Pain Intensity scale for SF-MPQ" OR "Revised Fibromyalgia Impact Questionnaire" OR "McGill Pain Questionnaire" OR "Wong-Baker FACES Pain Scale" OR "Neck Pain and Disability Scale" OR "Color Analog Scale" OR "Mankoski Pain Scale" OR "Brief Pain Inventory" OR "Descriptor Differential Scale of Pain Intensity" OR "Oswestry Disability Index" OR

"Numeric Rating Scale" OR "Alder Hey Triage Pain Score" OR "Behavioral Pain Scale" OR "Critical-Care Pain Observation Tool" OR "Dallas Pain Questionnaire" OR "Dolorimeter Pain Index" OR "Global Pain Scale" OR "Lequesne algofunctional index" OR "Multiple Pain Rating Scales" OR "Numerical 11 point box" OR "Roland-Morris Back Pain Questionnaire" OR "Wharton Impairment and Pain Scale")

S12 AB("constant-murley score" OR "Short form of McGill Pain Questionnaire" OR "Pain intensity Visual analogue scale for SF-MPQ" OR "Present Pain Intensity scale for SF-MPQ" OR "Revised Fibromyalgia Impact Questionnaire" OR "McGill Pain Questionnaire" OR "Wong-Baker FACES Pain Scale" OR "Neck Pain and Disability Scale" OR "Color Analog Scale" OR "Mankoski Pain Scale" OR "Brief Pain Inventory" OR "Descriptor Differential Scale of Pain Intensity" OR "Oswestry Disability Index" OR "Numeric Rating Scale" OR "Alder Hey Triage Pain Score" OR "Behavioral Pain Scale" OR "Critical-Care Pain Observation Tool" OR "Dallas Pain Questionnaire" OR "Dolorimeter Pain Index" OR "Global Pain Scale" OR "Lequesne algofunctional index" OR "Multiple Pain Rating Scales" OR "Numerical 11 point box" OR "Roland-Morris Back Pain Questionnaire" OR "Wharton Impairment and Pain Scale")

S13 TM("constant-murley score" OR "Short form of McGill Pain Questionnaire" OR "Pain intensity Visual analogue scale for SF-MPQ" OR "Present Pain Intensity scale for SF-MPQ" OR "Revised Fibromyalgia Impact Questionnaire" OR "McGill Pain Questionnaire" OR "Wong-Baker FACES Pain Scale" OR "Neck Pain and Disability Scale" OR "Color Analog Scale" OR "Mankoski Pain Scale" OR "Brief Pain Inventory" OR "Descriptor Differential Scale of Pain Intensity" OR "Oswestry Disability Index" OR "Numeric Rating Scale" OR "Alder Hey Triage Pain Score" OR "Behavioral Pain Scale" OR "Critical-Care Pain Observation Tool" OR "Dallas Pain Questionnaire" OR "Dolorimeter Pain Index" OR "Global Pain Scale" OR "Lequesne algofunctional index" OR "Multiple Pain Rating Scales" OR "Numerical 11 point box" OR "Roland-Morris Back Pain Questionnaire" OR "Wharton Impairment and Pain Scale")

S14 S8 OR S9 OR S10 OR S11 OR S12 OR S13

S15 S7 AND S14

S16 TI (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR AB (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR KW (((systematic OR state-of-the-art OR scoping OR literature OR umbrella) W0 (review OR reviews OR overview* OR assessment*)) OR "review* of reviews" OR meta-analy* OR metaanaly* OR ((systematic OR evidence) N1 assess*) OR "research evidence" OR metasynthe* OR meta-synthe*) OR MH ("Review Literature as Topic" OR "Review" OR "Meta-Analysis as Topic" OR "Meta-Analysis" OR "systematic review")

S17 S15 NOT S16

Appendix A2 Inclusion and exclusion criteria

1. Inclusion criteria met to proceed to full-text screening:

To include studies of the stated design, using a cognitive screen listed below, that includes a sample experiencing chronic pain.

Details of this criteria:

To include studies of the stated design:

- involving adults (18 years or older)
- written and printed in English
- involving multiple participants, for instance single group, case-control, cohort and comparative designs. Groups will be defined by pain status with cognitive screen performance as an outcome measure; groups defined by cognitive status will not be included.
- Longitudinal or intervention studies will be included but ordinarily the relevant data will be that from the study's baseline phase (pain status and cognitive screen).

using a cognitive screen listed below

Addenbrooke's Cognitive Examination (all versions: ACE, ACE-R, ACE-III, Mini-ACE)
Abbreviated Mental Test
Mini-Cog
Montreal Cognitive Assessment
Mini Mental State Examination
6-item cognitive impairment test
Hopkins Verbal Learning Test (including Revised version)
Test for the Early Detection of Dementia
Test Your Memory Test

- A study that includes one of the listed cognitive screens in title/abstract will meet this criterion.
- Any study where it can be identified within title/abstract that the only link to a cognitive screen is erroneous (e.g. an acronym contained in the abstract is identical to a test acronym but clearly refers to something else) <u>does not meet</u> this criterion.
- Outside of these two conditions the study will require full-text review as to whether the cognitive screen is present. This includes studies identified elsewhere (e.g. another article) as potentially involving one of the listed cognitive screens.

That includes a sample experiencing chronic pain:

Chronic pain is defined as Chronic pain is defined as

a) experiencing pain at one or more locations for over 3 months at the time of involvement in the study, or
b) diagnosis with a condition known to involve chronic pain, such as fibromyalgia, arthritis and rheumatic conditions. A fuller list of diagnoses determining chronic pain can be found in Appendix A2.4.
    - If there is no indication of a chronicity to the pain experienced by the sample and the condition is not a chronic pain condition, then the study does not meet this inclusion criterion.
    - If neither chronicity nor condition can be determined from title-abstract then the study will require full-text review as to whether either criteria for chronic pain are met.

2. Inclusion criteria for passing full-text screening

Cognitive screen data is retrievable for at least a chronic pain sample and a comparison sample

Details of this criteria:

chronic pain sample

The inclusion criteria remain as above – verification that the chronic pain sample is

c) experiencing pain at one or more locations for over 3 months at the time of involvement in the study, or
d) diagnosed with a condition known to involve chronic pain, such as fibromyalgia, arthritis and rheumatic conditions. A fuller list of diagnoses determining chronic pain can be found in Appendix A2.4.

When multiple clinical samples are presented in a study that potentially meet these criteria, at least one must meet the criteria. If more than one meet the criteria this must be considered at data analysis as per the protocol guidance on managing unit of analysis problems.

The study must also include one or more *comparison sample* that is not defined as experiencing chronic pain. If more than one sample fits this definition, one may be selected as the comparison if it introduces fewer confounding variables, for example a healthy control group would be chosen over a group who have recently been discharged from hospital due to a life-threatening illness. If there are multiple samples that are equally appropriate, they may all be involved by following the protocol guidance on managing unit of analysis problems.

Cognitive screen data is retrievable

The article must provide one or more of the following:

1. raw or summary cognitive screen data for at least one chronic pain and one comparison group, e.g. mean and standard deviation
2. correlations on the relationship between cognitive screen score and pain rating within a sample experiencing chronic pain
3. prevalence rates of cognitive impairment defined with reference to scores on a cognitive screen

A study that meets criteria 1 can provide data for a meta-analysis of effect size based on mean difference.

A study that meets criteria 2 can provide data for a meta-analysis of effect size based on pooled correlation coefficient. Note this may include studies that only provide cognitive screen data on a chronic pain sample (no comparison group).

A study that meets criteria 3 can provide data for a summary of cognitive impairment rates. Note this may include studies that only provide cognitive screen data on a chronic pain sample (no comparison group).

An article that indicates that cognitive screen data was collected but does not present it in any of the 3 formats described above may meet the inclusion criteria. The review team will determine whether the group-level data can be extrapolated from what is presented. If not, study authors will be contacted to explore access to data.

Requests to author: requests to author will be made using a pro-forma email request from a university email address. If no response is forthcoming after one week a brief follow-up request will be sent. If no response is forthcoming after a further week the data will be deemed inaccessible and analysis will commence without it.

Exclusion criteria

A study must be excluded if any stage of review determines

- relevant data depends on samples with a diagnosed cognitive impairment due to a disease with its origin in the brain, such as stroke, traumatic brain injury or dementia.
- the study is not published in the English language
- the study does not involve adult human subjects
- the study is a single participant case study

Appendix A2.4: Chronic Pain Conditions

Where pain is referenced but the chronicity is not possible to determine the review will consider the population to be experiencing chronic pain if the condition can be found on the lists of pain syndromes developed by the International Association for the Study of Pain (Classification of Chronic Pain, Second Edition Revised) lists 1A, 1F, 1H). These lists can be found at

https://www.iasp-pain.org/publications/free-ebooks/classification-of-chronic-pain-second-edition-revised/

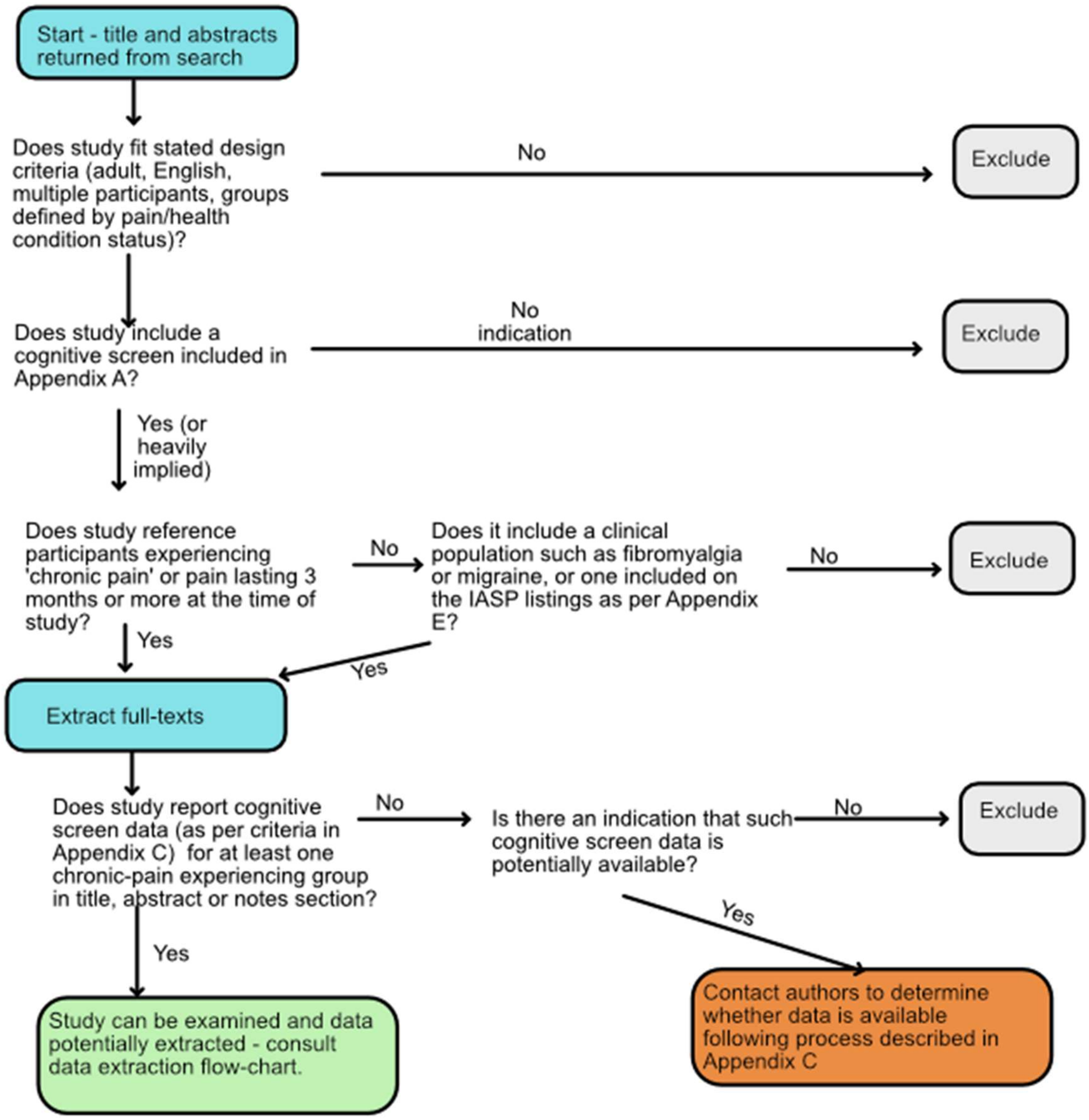
Specifically:

https://iaspfiles.s3.amazonaws.com/production/public/2021/PART_I-A.pdf

https://iaspfiles.s3.amazonaws.com/production/public/2021/PART_I-F.pdf

https://iaspfiles.s3.amazonaws.com/production/public/2021/PART_I-H.pdf

Appendix A2.5 – Decision flowchart for screening



A study will be excluded if any stage of review determines:

- the presence of a diagnosed cognitive impairment such as stroke, traumatic brain injury dementia or any other disease-related change expected to have an impact on cognition in a single group study, or within cases and not controls (or vice-versa) in studies using comparisons
- the study is not published in the English language
- the study does not involve adult human subjects
- the study is a single participant case study

Appendix A3 Meta-analysis code and reference materials

This link accesses an OSF project component containing R scripts and Rmarkdown document for the analysis within and creation of Chapter 1, together with a data dictionary of relevant variables extracted.

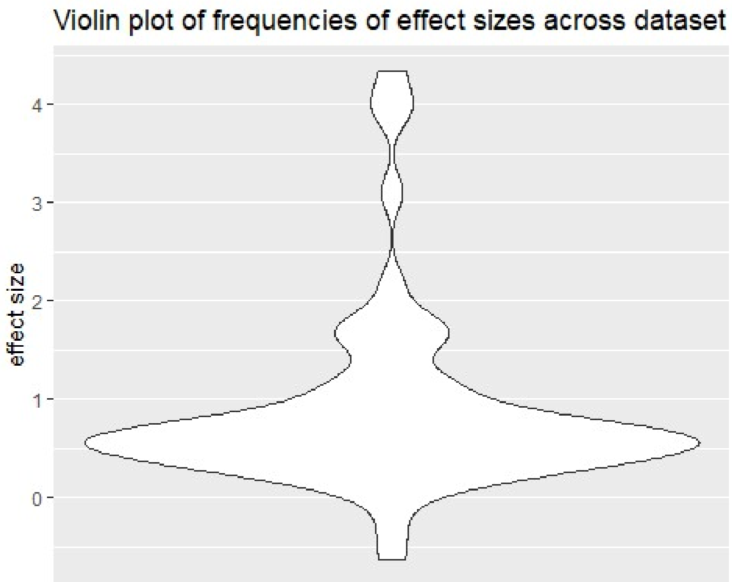
https://osf.io/hwa4j/

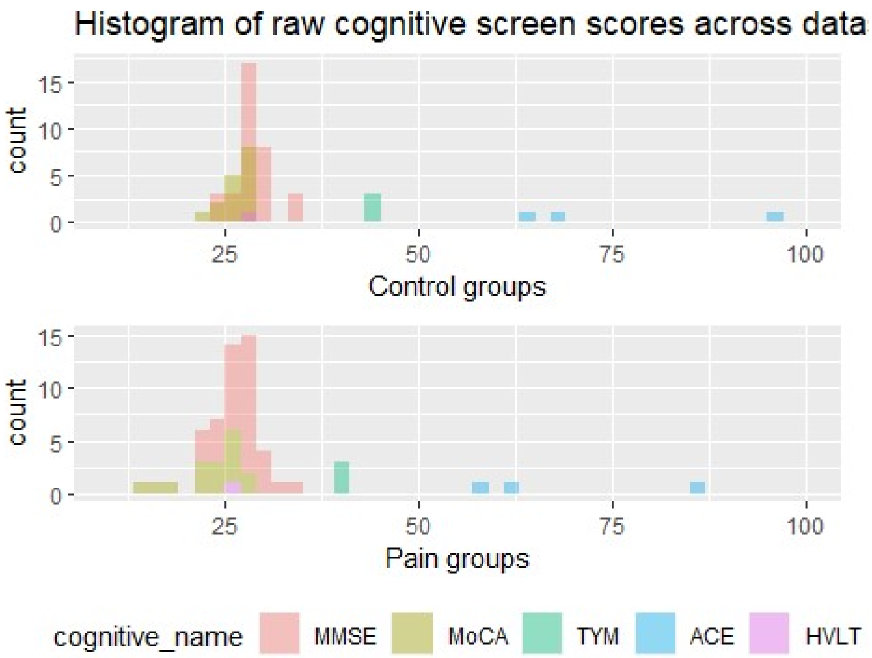
Appendix A4 Supplementary information to aid risk of bias assessment

JBI Item No	JBI Item Description	Supplementary Information
1	Were the criteria for inclusion in the sample clearly defined?	Inclusion and exclusion criteria reported for patients and controls - ideally patients defined by diagnostic criteria and reporting presence of pain for 3+months (or explicit in criteria)
2	Were the study subjects and the setting described in detail?	Reports source of subjects and demographics, study location, preferably time period
3	Was the exposure measured in a valid and reliable way?	Was pain measured at time of study using a validated tool? In both controls and patients?
4	Were objective, standard criteria used for measurement of the condition?	NA – no operationalisation that did not repeat 3
5	Were confounding factors identified?	Education, Age, Medication, Mood should all be reported
6	Were strategies to deal with confounding factors stated?	Education and Age should be addressed – Medication and Mood deemed to be too entangled to control for
7	Were the outcomes measured in a valid and reliable way?	Who administered the test, and what was the setting? Any alterations to the test described that were not validated in any way?
8	Was appropriate statistical analysis used?	Were means and sds or medians and iqr1 and 2 reported? (NB if no available information would lead to exclusion) Was a screen employed that differentially screened one group only (eg controls), or at a high level (e.g. MMSE 24+)

Appendix A5 Supplementary analyses (SR)

Supplementary exploratory information





Approach to dealing with multiple comparisons

Some studies offered more than one relevant comparison leading to extraction of multiple effect sizes in these cases. Supplementary Table 1 summarises which studies provided multiple estimates.

In three studies, multiple groups were compared against the same set of healthy controls: Fayed et al. (2012) for Fibromyalgia and Somatisation disorder, Peterson et al. (2018) for Rheumatoid arthritis (active), and Rheumatoid arthritis (controlled), with Ojeda et al. (2016) involving groups for Neuropathic chronic non-malignant pain, MSK chronic non-malignant pain and Fibromyalgia. As the control group data was used repeatedly for these comparisons, the effect size estimates are correlated (due to the correlation of the sampling error of these estimates).

In addition, Ojeda et al. (2016) used multiple screens, the MMSE and Test Your Memory. The remaining multiple comparisons involved a single control group and patient group for both the MMSE and MoCA - Chen et al. (2016) Vitturi et al. (2019).

One further study, Terassi et al. (2021) involved two separate pain groups each with a matched control group. The factor differentiating these pairs was a variable not relevant to this review (whether the individuals acted as caregivers) and the decision was made that this source of data would be better incorporated into the model as a single pair; accordingly these were merged into a single set of values (M and SD).

Supplementary Table A1.

Authors	MMSE	MoCA	TYM	ACE
Fayed et al. (2012)	Fibromyalgia			
Fayed et al. (2012)	Somatisation disorder			
Peterson et al. (2018)	Rheumatoid arthritis (active)			
Peterson et al. (2018)	Rheumatoid arthritis (controlled)			
Ojeda et al. (2016)	Neuropathic chronic non-malignant pain			
Ojeda et al. (2016)	MSK chronic non-malignant pain			
Ojeda et al. (2016)	Fibromyalgia			
Ojeda et al. (2016)			Neuropathic chronic non-malignant pain	
Ojeda et al. (2016)			MSK chronic non-malignant pain	
Ojeda et al. (2016)			Fibromyalgia	
Chen et al. (2016)		Chronic migraine		
Chen et al. (2016)	Chronic migraine			
Liao et al. (2018)		Knee osteoarthritis		
Liao et al. (2018)	Knee osteoarthritis			
R. Wang et al. (2014)		Cluster headache		
R. Wang et al. (2014)	Cluster headache			
Vitturi et al. (2019)		Rheumatoid arthritis		
Vitturi et al. (2019)	Rheumatoid arthritis			
Terassi et al. (2021)				Non-caregiver with chronic pain
Terassi et al. (2021)				Caregivers with chronic pain

Correcting for multiple comparisons

To deal with data interdependency, a Correlated Hierarchical Effects (CHE) model was utilised. As part of this workflow, a variance-covariance matrix was computed across all the comparisons (dimensions 62 * 62) using the vcalc() function from the *metafor* pacakage. In such a matrix, the diagonal (identity) composed of the sampling variance of each study (eg, element [6,6] would contain the sampling variance for comparison 6). If that comparison is unrelated to others, only this element will be used to stand-in for the study sampling variance (meaning the study sampling variance remains the study sampling variance). When groups are related the vcalc() process will produce covariance estimates of the two (sampling variances) at the appropriate positions (e.g., if studies 7 and 8 share a control group, matrix elements [7,8] and [8,7] will incorporate these covariance estimates). This is further shaped by a correlation matrix based on published relationships between cognitive screens: MoCA with MMSE (Nasreddine et al., 2005), MMSE with ACE (ACE-III) (Matias-Guiu et al., 2017), MMSE with TYM (Zande et al., 2017). Other relationships were estimated but are not actually required as these relationships are not relevant for these studies.

```
##       MMSE  MoCA  TYM   ACE HVLT
## MMSE 1.000 0.870 0.77 0.877 0.75
## MoCA 0.870 1.000 0.75 0.679 0.75
## TYM  0.770 0.750 1.00 0.750 0.75
## ACE  0.877 0.679 0.75 1.000 0.75
## HVLT 0.750 0.750 0.75 0.750 1.00
```

For eg Liao et al. (2018), with one MMSE and one MoCA comparison on identical groups, the matrix elements are:

```
V[dfm_mod$study_num == 121, dfm_mod$study_num == 121]

##           [,1]       [,2]

## [1,] 0.0712071 0.06229010

## [2,] 0.0622901 0.07199068
```

and the underlying correlation matrix is, as expected,

```
cov2cor(V[dfm_mod$study_num == 121, dfm_mod$study_num == 121])

##      [,1] [,2]

## [1,] 1.00 0.87

## [2,] 0.87 1.00
```

Model calculation then draws on this V matrix to inform the final weighting of comparisons; the effect is a downweighting of estimates from studies with multiple comparisons. See the comparable process documented at https://wviechtb.github.io/metadat/reference/dat.knapp2017.html. Results from this process are reported in the results of chapter 1.

RVE calculation

An additional model was conducted using a robust variation estimation (RVE) approach introduced as a final step to the CHE workflow described above. This introduces a Sandwich estimator that can be superior in estimating standard errors and thus the confidence intervals around the effects produced. This can be beneficial in clustered datasets particularly when the number of clusters is small. In our case, the model outputs were almost identical to the original multi-level approach, and was therefore not pursued further. See model outputs:

CHE-only approach:

```
che.model

##

## Multivariate Meta-Analysis Model (k = 62; method: REML)

##

## Variance Components:

##

##              estim    sqrt  nlvls  fixed               factor


## sigma^2.1  0.2505  0.5005     51     no            study_num


## sigma^2.2  0.1476  0.3842     62     no  study_num/unique_id


##

## Test for Heterogeneity:

## Q(df = 61) = 481.8993, p-val < .0001

##

## Model Results:

##

## estimate      se    tval  df    pval   ci.lb   ci.ub     <U+
```

```
200B>
##   0.7606  0.0953  7.9779  61  <.0001  0.5699  0.9512  ***
##
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
 1
```

RVE approach:

```
rve.model

##

## Multivariate Meta-Analysis Model (k = 62; method: REML)

##

## Variance Components:

##

##              estim    sqrt  nlvls  fixed              factor

## sigma^2.1  0.2505  0.5005     51     no           study_num

## sigma^2.2  0.1476  0.3842     62     no  study_num/unique_id

##

## Test for Heterogeneity:

## Q(df = 61) = 481.8993, p-val < .0001

##

## Number of estimates:   62

## Number of clusters:    51

## Estimates per cluster: 1-6 (mean: 1.22, median: 1)

##

## Model Results:

##

## estimate     se¹   tval¹    df¹   pval¹  ci.lb¹  ci.ub¹
<U+200B>

##   0.7606  0.0952  7.9881  48.79  <.0001  0.5692  0.9519  ***

##

## ---

## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' '
```

```
 1
##
## 1) results based on cluster-robust inference (var-cov estima
tor: CR2,
##    approx. t-test and confidence interval, dfs = Satterthwai
te method)
```

References

Matias-Guiu, J. A., Valles-Salgado, M., Rognoni, T., Hamre-Gil, F., Moreno-Ramos, T., & Matías-Guiu, J. (2017). Comparative diagnostic accuracy of the ACE-III, MIS, MMSE, MoCA, and RUDAS for screening of alzheimer disease. *Dementia and Geriatric Cognitive Disorders*, *43*(5-6), 237–246. https://doi.org/10.1159/000469658

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Zande, E. van de, Cornelis Maria van de Nes, J., Jansen, I., Nouelle van den Berg, M., Floor Zwart, A., Bimmel, D., … Andringa, G. (2017). The test your memory (TYM) test outperforms the MMSE in the detection of MCI and dementia. *Current Alzheimer Research*, *14*(6), 598–607. https://doi.org/10.2174/1567205013666161201202520

Application ID: 11332

Project details | Collaborators | Payments | Requests | Admin | Messages | Data

Institutes and colleagues involved

Please be advised that only researchers who are already registered and approved can be added as collaborators to applications.

Please select Institute where you will be conducting the project

University of Glasgow

Principal investigator

Breda Cullen (breda.cullen@glasgow.ac.uk)

Collaborator

Alexander Fradera (2509920F@student.gla.ac.uk)

☐ Delegate

Remove Person

Collaborator

Andrew Schrepf (Andrew.Schrepf@glasgow.ac.uk)

☐ Delegate

Remove Person

Appendix B2 Analysis code and reference materials

This link accesses an OSF project component containing R scripts and Rmarkdown document for the analysis within and creation of Chapter 2, together with a data dictionary of relevant variables extracted.

https://osf.io/cmfkp/

MRP Proposal

How is the prediction of dementia using cognitive scores affected by comorbid pain?

2021-05-07

V4.1

3894 words

Abstract

Background

Cognitive tests are routinely used to identify whether an individual may have a dementing illness. Scores are not typically adjusted for factors that can affect cognitive performance such as pain, a health issue prevalent in middle aged and older adults. Using a large general population cohort with data regarding dementia diagnosis, pain and cognitive scores, the present study seeks to understand how identification of dementia via cognitive information is affected by the presence of pain.

Aims

To determine how the presence of pain affects the accuracy of a model that predicts dementia based on a cognitive score that draws on multiple domains of cognition (processing speed, retrospective and prospective memory, and reasoning).

Methods

A nested case-control analysis will be conducted within the large cohort dataset UK Biobank by identifying cases (individuals who have developed dementia within a window following cognitive testing) and matching them demographically to dementia-free controls. A series of conditional logistic regression models will then explore the impact of pain on model performance. Pain will be measured via self-report with supplementary analyses looking at other indicators of pain (pain medication and painful medical condition).

Applications

This study will contribute to the understanding of the impact of pain on accuracy of dementia identification (overall dementia, Alzheimer's, and Vascular dementia) using cognitive measures. This can inform approaches in clinical settings such as accounting for comorbid pain when investigating dementia with cognitive tests, as well as future development of epidemiological tools.

Introduction

Early diagnosis of dementia is crucial to support those affected by the disease and is often prioritised by government policy (e.g. The Scottish Government, 2010). NICE guidance recommends the use of cognitive testing as part of the diagnosis process (Duff, 2018). Initially this would involve a short cognitive screening instrument such as the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) or Addenbrooke's Cognitive Examination III (ACE-III, Hsieh et al., 2013); ambiguous cases may then be assessed using lengthier test batteries. Cognitive measures inform diagnosis by generating scores that are appraised relative to benchmarks or thresholds. This provides benefits of standardisation and simplicity, especially for screening instruments which combine information across cognitive domains into a single score. However such approaches give little allowance for factors unrelated to organic brain disease that may influence the results.

One such factor is pain, an experience increasingly prevalent as we age (Blyth et al., 2001) whose impact on cognition is described in a review by Moriarty et al. (2011). This details evidence that individuals suffering chronic pain experience difficulties with attentional tasks; memory issues including poorer performance on spatial and verbal tasks; slower reaction time on speeded cognitive tests; and potentially impaired executive functioning including planning and controlled behaviour. Scores on screening tests such as the MoCA have been shown to be lower in samples experiencing pain (see e.g. Ferreira et al., 2016), meaning that pain may bring individual scores below clinical thresholds for dementia, producing false positive diagnoses. However, this has not been directly investigated. This study aims to address this using an existing dataset, the UK Biobank.

UK Biobank

Launched in 2006, the UK Biobank “is a large-scale biomedical database and research resource, containing in-depth genetic and health information from half a million UK participants” (UK Biobank, 2021a, sec. 1). This prospective cohort study monitors health records for its participants to capture reports of ICD diagnoses including dementia; at the time of writing 5799 UK Biobank participants who were free of dementia at baseline had subsequently received that diagnosis.

UK Biobank contains extensive clinical information including pain measures as well as a set of measures that provide snapshots of four cognitive domains (prospective memory, processing speed, visual memory, and verbal-numerical reasoning). These are significant predictors of future dementia diagnosis over and above established risk factors such as hypertension or a family history of dementia (Calvin et al., 2019). While that study concerned forecasting dementia up to eight years into the future, it seems plausible that these measures would also have some ability to identify dementia over timescales closer to those involved in clinical investigations. If so it will be possible to then ask whether and to what extent the presence of pain interferes with dementia identification. This is the aim of this study.

Aims and Research Questions

The principal aim of this study is to investigate the impact of pain on the accuracy of a set of measures for identifying dementia that emerges within clinically meaningful timescales (quantified below). This will be addressed via the following questions:

1. How effectively do the UK Biobank cognitive measures discriminate future dementia cases from non-cases?
2. How is the model discrimination affected by pain? Specifically,
    1. Does comorbid pain increase the likelihood of an erroneous classification of dementia (by applying some form of diagnostic cut-off) on the basis of cognitive test scores? If so, to what degree?
    2. Does comorbid pain weaken the relationship between cognitive testing scores and dementia status, meaning that scoring high or low provides less insight for diagnosis? If so, to what degree?

These subquestions help us understand the consequences that comorbid pain may have for the use of cognitive scores both when employing a threshold for classification (2.1) or otherwise (2.2).

Secondary research questions are:

3. Is the impact of pain on model discrimination different for different dementia subgroups (e.g. Alzheimer’s disease versus vascular dementia)?
4. Is model discrimination and the impact of pain different for different age-groups?

These questions help specify relative impact of pain on diagnostic accuracy for different populations.

Design, Methods and Procedure

This will be a nested case-control study drawing on existing data from the UK Biobank.

Participants

All participants will be drawn from the UK Biobank and comprise individuals with a diagnosis of dementia (cases) and matched controls without dementia according to the most recent follow-up data.

Inclusion and Exclusion criteria

Eligible cases will have a diagnosis of dementia that was first recorded subsequent to an assessment visit at which they completed the cognitive measures. As UK Biobank participation was limited to those younger than 70 at baseline, we anticipate that compared to the prevalence within the general population, this dataset will include proportionately more young onset dementia cases (diagnosis before 65), a group for whom early detection is particularly important (Jefferies & Agrawal, 2009) but misdiagnosis is common (Rossor et al., 2010).

The analysis from Calvin et al. (2019) suggests the measures have predictive power up to eight years into the future, but a clinically meaningful window is better suggested by Vliet et al. (2013). This team investigated time from onset of dementia symptoms to dementia diagnosis, finding that on average 2.8 (for late-onset) and 4.4 years (for young-onset) passed between symptom development and diagnosis, with their combined sample experiencing an average duration of 3.8 years. The current study will look at diagnosis up to four years after the administration of the cognitive and pain measures, that is, 1-48 months.

Controls will be matched to the cases in a 3:1 ratio based on matching variables (see below) and the presence of assessment data from the same timepoint. The matching process will be governed by software (e.g. vMatch) and strictness of matching will be determined by the constraints of the dataset.

Cases and controls will be excluded where there was a clear non-dementia organic cause for cognitive impairment (such as non-progressive brain injuries) at the time tests were completed. Controls will lack a diagnosis of dementia at any point up until the most recent follow-up data at time of analysis.

Data access procedures

The UK Biobank resource exists for “bona fide researchers ….to conduct health-related research that is in the public interest” (UK Biobank, 2021b, sec. 2). Researchers apply to access the dataset and those accepted then register their programmes of work with the central UK Biobank team. Data is then available in the form of data extracts composed of the relevant variables.

Measures

Incident Dementia

UK Biobank is updated with information from a range of healthcare contexts (e.g. death register, hospital inpatient records). This study will draw on the First Occurrences fields, which provide the first time an ICD10-coded diagnosis was recorded for that participant, to capture incident dementia and dementia subtype (Alzheimer’s, Vascular or unspecified dementia).

Cognitive Measures

A summary of the four cognitive measures is shown in Table 1. Each test was developed for UK Biobank and their test designs are distinct from classical tests that they may otherwise resemble. All measures except verbal-numerical reasoning were designed with reference to validated tests and were assessed for validity and reliability; in addition three of the tests (visual memory, prospective memory and verbal-numerical reasoning) correlate with the Mini-ACE dementia assessment, r between .27 and .35 (Fawns-Ritchie & Deary, 2020).

Table 1: UK Biobank cognitive measures used for predicting dementia diagnosis.

Test	Description	Scoring
Visual memory	Memorising the position of different symbols shown on cards, which are then shown face-down. Participant must select pairs with matching symbols in as few attempts as possible.	Errors made
Prospective memory	At the end of the cognitive section, participants are presented with instructions but must remember to apply a change to the instructions given to them earlier.	1 if correct response, 0 for mistake
Verbal-numerical reasoning	Multiple-choice problems tapping logical and reasoning ability in verbal and numerical domains.	Score between 0 and 13
Reaction time	Akin to the game "Snap", participants must quickly press a button-box whenever two identical cards are shown on-screen.	Mean time of matches (ms)

Participants completed these measures on a touchscreen device at each in-person visit to UK Biobank, with no involvement from staff. The baseline visit acquired data from upwards of 160,000 participants (later visits provided fewer data). For the purposes of this study the four measures will be combined into a general score (see analysis plan).

Pain

The UK Biobank dataset offers a variety of ways to operationalise pain status.

Self-report survey: A previous study using UK Biobank data (Allen et al., 2020) used self-report survey responses to create a dichotomous variable for chronic pain (considered by the ICD as pain continuing for at least 3 months, Allen et al., 2020). Participants were asked “In the last month have you experienced any of the following that interfered with your usual activities?” with a list of pain locations e.g. “back pain”. This was deemed as chronic if the patient replied affirmatively to a follow-up question “have you had [… pain] for more than 3 months?”. Over 215k participants indicated some form of chronic pain at baseline assessment.

Pain medication: At assessment visits participants provided medication information, including those prescribed for clinical levels of lasting pain. This will be used to create a dichotomous variable indicating use of one or more of such medications.

Painful condition: A dichotomous variable will also be created for presence of a painful medical condition such as arthritis, using ICD codes of first occurrences (as described above).

Analyses will use the self-report survey data on chronic pain as the main pain variable.

Matching variables

The matching of cases to controls will be guided by demographic information: age, sex, level of educational attainment (degree versus no degree).

Research procedures

Data was collected by UK Biobank at a number of time points, with all participants completing at least one in-person visit to an assessment centre. Data was collected in a standardised fashion using computer touch-screens to complete cognitive tests and questionnaires. The cognitive tests were short and could be completed within around 10 minutes.

Ethics, Governance and Data Protection

This study involves drawing data from the UK Biobank. All participants gave written informed consent and are free to withdraw their data at any time. All data are anonymised centrally and an individual’s data points are identified only by an identity code, with the identity log held centrally by UK Biobank and not shared with researchers. Use of UK Biobank data does not require project-specific ethical approval due to pre-existing approval as a research tissue bank from the NHS National Research Ethics service.

The Principal Investigator and other members of the research team who have been approved by the UK Biobank central office will have access to the data and upon completion of the study, the data will be stored securely in accordance with the Material Transfer Agreement between the University of Glasgow and UK Biobank.

NHS R&D approval is not required for UK Biobank research but NHS employees are required to notify their local R&D department that they are conducting such research.

Analysis Plan

This study will take a conditional logistic regression approach, using an individual-level matched design. Conditional logistic regression is a variation of logistic regression which takes account of the matched nature of the dataset.

Preliminary steps

Data from the UK Biobank will be extracted and processed in stages. Stata software will be used by one member of the research team to identify cases and controls in order to create the nested dataset for analysis. This will be passed to the primary researcher who will use RStudio for data cleaning (including identification of missing values), wrangling, and subsequent analysis.

Scores from the four cognitive measures will be combined into a composite score, analogous to the single total scores generated by clinical cognitive screens. Fawns-Ritchie & Deary (2020, p. 14) used Principal Components Analysis (PCA) to combine these scores (together with a discontinued working memory measure) into a general cognitive ability measure shown to correlate with the Mini-ACE cognitive screen, and this study will follow this PCA-based method based on the case-control dataset.

Primary analyses

A) Within the regression analysis, the first step will be to regress dementia status (i.e. case or control) upon the general cognitive score. This addresses research question 1.

B) To address research question 2.1 the regression model will be used to identify a threshold for the cognitive score that maximises correct identification of dementia. This will be achieved using a Receiver-Operating Characteristic curve analysis. This cut-off will be applied to categorise the dataset, and this categorisation can then enable the identification of the characteristics of those who are correctly and falsely identified, including differences in participants with and without co-morbid pain, as depicted in Figure 1; this can be statistically investigated using Chi-square analysis.

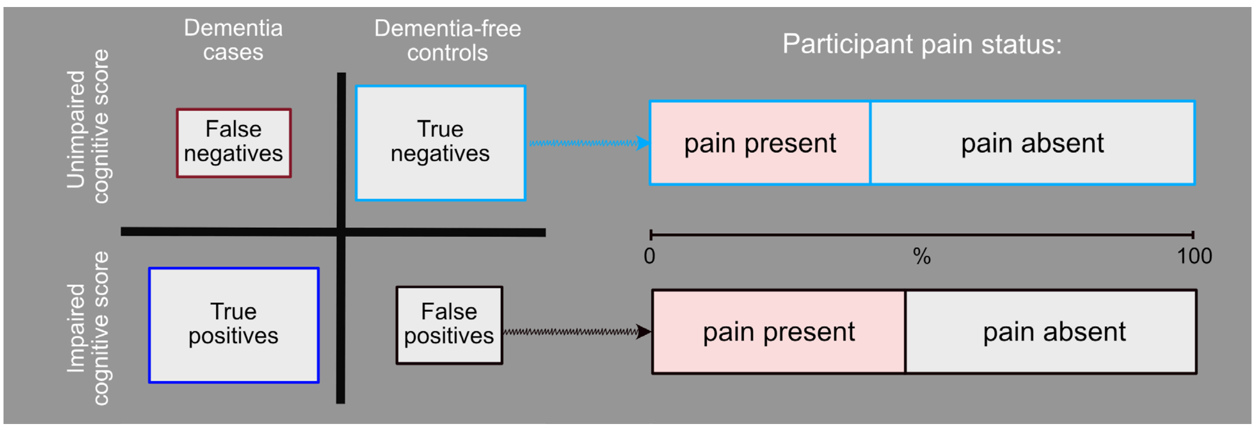


Figure 1: Left: Hypothetical discrimination of the optimised regression model. Right: Hypothetical breakdown of participant pain within different discrimination categories

C) To address research question 2.2 the model will be developed with additional regressors.

i) Self-reported chronic pain will be added to the model as a regressor. This reveals how pain is associated with the odds of dementia diagnosis (after accounting for cognitive score) and is a precursor to the next step.

ii) The next regressor is the interaction between cognitive score and pain. This reveals how much the association between cognitive score and dementia status varies according to pain status.

iii) If the interaction is significant, this calls for a further piece of analysis that manually derives stratified coefficients to address the primary research question more systematically. This will be to establish the odds ratio (OR) for dementia in those with poor versus good cognitive scores, once focusing on people with pain, and again for those without. This will be done using post-estimation 'lincom' commands.

Secondary analyses

A secondary analysis will run the steps described above with two subgroups: one using cases with Alzheimer's Dementia and one cases with Vascular Dementia (and corresponding matched controls). This will allow us to see whether model performance varies according to dementia type and the impact that pain experience has on this.

Data permitting, a secondary analysis will take the same approach with age-based subgroups: older cases (65+ at time of diagnosis) with matched controls, and younger cases (under 65 at time of diagnosis) with matched controls.

Sensitivity analyses

Data permitting, the study will analyse a dementia subgroup with 1-24 months between test-taking and diagnosis, to see whether this produces an improved model.

Analyses will be repeated replacing the self-reported chronic pain variable with (i) presence of pain medication and (ii) presence of a painful condition. This will see whether these alternative criteria for pain produce clearer effects.

Sample Size and power calculation

962 participants received a dementia diagnosis within 48 months of completing the cognitive measures. Matching three controls to each case, while recognising the reality of missing data, we anticipate it will be possible to create a dataset of approximately 3000 participants. The package EpiR (Stevenson et al., 2021) provides sample and power calculations for matched case-control studies using an approach developed by Dupont (1988). This was used to calculate the smallest odds ratio possible to reliably detect in this model while maintaining a power of 80%. With 3000 participants and an assumed correlation (rho) between pain presence cases and their matched controls of .3, an analysis would be able to detect an odds ratio of at least 1.33 at 95% confidence interval (i.e. alpha = 0.05). However the key effect of interest is an interaction, and statisticians suggest an interaction effect size is often around half the main effect size (Gelman, 2018). For the study to be detecting an OR of 1.33 for the interaction, the main effect OR would thus need to be at least 1.77. UK Biobank was designed to be able to assess effects of this scale, which are considered (within the context of public health) to be small but still clinically meaningful (Sudlow et al., 2015).

Timetable

2021	January - April 5th	Proposal prepared / submitted for blind review

2021	April 30th - June 15th	Final approved MRP proposal and Ethics Letter submitted
2021	July-August	Full explication of analysis plan
2021	September-October	Development / running of PCA analysis
2021/2	November-December	Development / testing of analysis scripts
2022	January-February	Data analysis
2022	March-May	Write up of thesis
2022	June-July	Thesis revisions and submission

Health and Safety

This study will be working purely with a pre-existing dataset, which constitutes limited risks to the investigators. The student investigator conducting the analyses will be accessing data according to the requirements put in place by the UK Biobank and will be registered with the project prior to accessing any data.

Equipment and costs

There are no costs or equipment implicated in this study. All data storage, processing and analysis will occur on existing equipment and software.

Practical Applications and Dissemination

This study aims to identify whether prediction of dementia using a short battery of cognitive measures is affected by comorbid pain.

Although the UK Biobank cognitive tool is not in clinical use it correlates with the Mini-ACE and addresses cognitive domains considered in dementia assessment. The measures of misdiagnosis that the study generates may inform clinical pathways, potentially distinguishing the risks for different services (e.g. Young Onset).

An advantage of using this large cohort dataset is the generation of precise and reliable estimates of effect size or odds ratio. This gives an indication of whether this may be a pressing concern or likely to be relatively minor in impact. This can inform further clinic-based research as well as current clinical decision-making, which may not consider the impact of pain or may involve informal adjustments/interpretation that are not driven by an evidence base.

In addition, this research may inform further development of the predictive model used by Calvin et al. (2019) and ensure it is more comprehensive and mindful of the impact of pain. The construction of a clear and reproducible analysis plan with shareable code will make it easier for subsequent research to build on.

After completion this study will be submitted to the University of Glasgow as a thesis submission for the student investigator’s Doctorate of Clinical Psychology course. During conduct of the study the investigators will assess possible routes to publication within the academic press and determine appropriate academic conferences.

UK Biobank has routes for dissemination of information to its participants, such as newsletters and research publicity events. The investigators will seek to engage with these routes to publicise findings to UK Biobank participants, upon whose efforts the study depends.

References

Allen, S. F., Gilbody, S., Atkin, K., & van der Feltz-Cornelis, C. (2020). The associations between loneliness, social exclusion and pain in the general population: A n= 502,528 cross-sectional UK Biobank study. *Journal of Psychiatric Research*, *130*, 68–74.

Blyth, F. M., March, L. M., Brnabic, A. J., Jorm, L. R., Williamson, M., & Cousins, M. J. (2001). Chronic pain in Australia: A prevalence study. *Pain*, *89*(2-3), 127–134.

Calvin, C. M., Wilkinson, T., Starr, J. M., Sudlow, C., Hagenaars, S. P., Harris, S. E., Schnier, C., Davies, G., Fawns-Ritchie, C., & Gale, C. R. (2019). Predicting incident dementia 3-8 years after brief cognitive tests in the UK Biobank prospective study of 500,000 people. *Alzheimer's & Dementia*, *15*(12), 1546–1557.

Duff, C. (2018). *Dementia: Assessment, management and support for people living with dementia and their carers (nice guideline 97).* National Institute of Clinical Excellence.

Dupont, W. D. (1988). Power calculations for matched case-control studies. *Biometrics*, *44*(4), 1157–1168. https://doi.org/10.2307/2531743

Fawns-Ritchie, C., & Deary, I. J. (2020). Reliability and validity of the UK Biobank cognitive tests. *PloS One*, *15*(4), e0231627.

Ferreira, K. S., Oliver, G. Z., Thomaz, D. C., Teixeira, C. T., & Foss, M. P. (2016). Cognitive deficits in chronic pain patients, in a brief screening test, are independent of comorbidities and medication use. *Arquivos de Neuro-Psiquiatria*, *74*(5), 361–366.

Gelman, A. (2018). You need 16 times the sample size to estimate an interaction than to estimate a main effect. [Blog] In *Statistical Modeling, Causal Inference, and Social Science*. Available at https://statmodeling.stat.columbia.edu/2018/03/15/need-16-times-sample-size-estimate-interaction-estimate-main-effect/

Hsieh, S., Schubert, S., Hoon, C., Mioshi, E., & Hodges, J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in frontotemporal dementia and Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *36*(3-4), 242–250. https://doi.org/10.1159/000351671 [doi]

Jefferies, K., & Agrawal, N. (2009). Early-onset dementia. *Advances in Psychiatric Treatment*, *15*(5), 380–388.

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology*, *93*(3), 385–404. https://doi.org/https://doi.org/10.1016/j.pneurobio.2011.01.002

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699.

Rossor, M. N., Fox, N. C., Mummery, C. J., Schott, J. M., & Warren, J. D. (2010). The diagnosis of young-onset dementia. *The Lancet Neurology*, *9*(8), 793–806.

Stevenson, M., Nunes, E. S. with contributions from T., Heuer, C., Marshall, J., Sanchez, J., Thornton, R., Reiczigel, J., Robison-Cox, J., Sebastiani, P., Solymos, P., Yoshida, K., Jones, G., Pirikahu, S., Firestone, S., Kyle, R., Popp, J., Jay, M., & Reynard., C. (2021). *EpiR: Tools for the analysis of epidemiological data*. https://CRAN.R-project.org/package=epiR

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., & Landray, M. (2015). UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *Plos Med*, *12*(3), e1001779.

The Scottish Government. (2010). *Scotland's National Dementia Strategy 2010-2013*. The Scottish Government.

UK Biobank. (2021a). *UK Biobank: About us* (03/07; Vol. 2021).

UK Biobank. (2021b). *UK Biobank: Register* (03/07; Vol. 2021).

Vliet, D. V., Vugt, M. D., Bakker, C., Pijnenburg, Y., Vernooij-Dassen, M., Koopmans, R., & Verhey, F. (2013). Time to diagnosis in young-onset dementia as compared with late-onset dementia. *Psychological Medicine*, *43*(2), 423–432.

Appendix 1: DATA MANAGEMENT PLAN (DMP)

Note:
This DMP template is adapted from the guidance provided here: https://www.gla.ac.uk/myglasgow/datamanagement/creatingyourdata/dataplanning/ Trainees should seek advice from their University Supervisor when developing the DMP. Examples of DMPs from different types of projects (including both quantitative and qualitative research) can be viewed here: https://www.dcc.ac.uk/resources/data-management-plans/guidance-examples The University of Glasgow data repository is Enlighten: http://researchdata.gla.ac.uk/

Title of project
How is the prediction of dementia using cognitive scores affected by comorbid pain?
What data will be created? • Note the type and amount of data that will be created, e.g. assessment scores; transcripts; etc • Explain how you will capture the data, e.g. paper record forms; online survey; spreadsheet • What file formats will you use and why? e.g. "Microsoft Excel will be used as it is in widespread use" (adapt such statements to suit your project)
This study involves drawing data from UK Biobank. The project has anonymised its dataset and an individual's data points are identified only by an anonymous code, with the log held centrally and not accessible by the research team. The variables that will be collected involve routinely collected health information and performance on cognitive measures, together with demographic and other information used to match participants. Where appropriate new variables will be created by recoding or transforming the data, for instance, creating a binary variable of pain experience/no pain experience based upon responses to multiple survey items. The data will be stored in Stata format (.dta) and .csv format.

How will the data be documented and described? • What contextual details are needed? e.g. a written description of the data collection and analysis methods; dictionary of variable labels and values (e.g. category labels) • How will you document this? e.g. in the project write-up; in a ‘readme’ text file alongside the dataset(s)
UK Biobank variables are accompanied by a data dictionary specifying what it refers to and collection time points. Where new variables are created, an additional data dictionary will be created to specify the origin and transformations involved in creating the new variables. These will exist in comments within the code and additionally as a separate readme.txt file. Where appropriate this will also be described within the project write-up.
How will you manage ethics, governance and intellectual property? • How will you safeguard the privacy of research participants? e.g. via informed consent (state if consent for future data sharing will be sought) • What organisational approvals will you obtain? • If any intellectual property is to be generated in the project, how will this be managed? e.g. if you are developing a novel questionnaire or a software app

This study involves drawing data from the UK Biobank. The project has anonymised its dataset and an individual's data points are identified only by an anonymous code, with the log held centrally and not accessible to the research team.

This study involves drawing data from the UK Biobank. All participants gave written informed consent and are free to withdraw their data at any time. All data are anonymised centrally and an individual's data points are identified only by an identity code, with the identity log held centrally by UK Biobank and not shared with researchers. Use of UK Biobank data does not require project-specific ethical approval due to pre-existing approval as a research tissue bank from the NHS National Research Ethics service.

NHS R&D approval is not required for UK Biobank research but NHS employees are required to notify their local R&D department that they are conducting such research.

No intellectual property will be generated by the project.

What are the plans for data sharing and access?

- Who is expected to use the completed dataset(s) and for what purpose?
- How will the data be developed with future users in mind? e.g. use of widely-used or open source file formats
- How will you make the data available? e.g. deposit in a data repository; forward copies on request; create website

The dataset will be used by the principal investigator as part of his doctorate thesis.

The project data itself cannot be made accessible in a data repository as the UK Biobank constituted an existing, controlled repository. The analytic approach will be reproducible from the analysis scripts in the form of .R files (open source and freely available). All code will be commented to ease with clarity of understanding and make re-use as simple as possible.

Any new derived variables will be returned to the UK Biobank central office for sharing with other approved researchers

What is the strategy for long-term preservation and sustainability?

- How will you store and back-up the data? e.g. University server with automatic back-up; University OneDrive account
- What are the plans for sustainability? e.g. choose open source file formats; deposit in data repository
- Which repository/data centre have you identified as a place to deposit your data? e.g. Enlighten; Open Science Framework
- How will you prepare data for preservation and sharing? Indicate the time and resource required for this
- How and when will you transfer ongoing responsibility for preservation/archiving to your University Supervisor?

Storage: The data will be stored on a University OneDrive account or network servers.

Sustainability: Although open-source file formats provide advantage, the use of them for data analysis can produce risks of non-reproducibility, as when for example an analysis package is updated to operate differently than how it was used at the time of the original analysis, as detailed at http://datacolada.org/95. A solution to this is to use effectively date-stamped versions of all functions, and an R package allowing this, Groundhog, will be used to do so.

Repository: code will be placed on researchbox.org, a platform optimised for “sharing data, code, materials and pre-registrations with their readers” in a way that is simplified and accessible.

The Principal Investigator and other members of the research team who have been approved by the UK Biobank central office will have access to the data and upon completion of the study, the data will be stored securely in accordance with the Material Transfer Agreement between the University of Glasgow and UK Biobank.

Appendix 2: RESEARCH EQUIPMENT, CONSUMABLES AND EXPENSES

Trainee ……………………………………………………………………

Year of Course ………2………………………. **Intake Year**……2019……………..

Please refer to latest **stationery costs** list and **departmental test** list (available on Moodle)

Item	Details and Amount Required	Cost or Specify if to Request to Borrow from Department
Stationery	0	Subtotal: 0
Postage	0	Subtotal: 0
Photocopying and Laser Printing	0	Subtotal:0
Equipment and Software	0	Subtotal:0
Measures	0	Subtotal:0
Miscellaneous	0	Subtotal:0
Total	0	

For any request over £200 please provide further justification for all items that contribute to a high total cost estimate. Please also provide justification if costing for an honorarium:

Trainee signature……………… Date…22/04/2021

University Supervisor signature … Date …30/03/21

Appendix 3: HEALTH AND SAFETY FOR RESEARCHERS

1. Title of project	How is the prediction of dementia using cognitive scores affected by comorbid pain?
2. Trainee	
3. University Supervisor	Jonathan Evans
4. Other Supervisor(s)	Breda Cullen
5. Local Lead Clinician	Lisa Gadon
6. Participants (age, group or sub-group, pre- or post-treatment, etc)	UK Biobank Participants
7. Procedures to be applied (e.g. questionnaire, interview, etc)	Modelling analysis of existing data
8. Setting i) Where will procedures be carried out?	At home/university
ii) Are home visits involved?	Y / <u>N</u>
9. Potential risk factors identified (see table overleaf) a. Participants b. Procedures c. Settings	No risk factors identified, given that • all participant contact /management falls to UK Biobank and outside the scope of this project • procedures are purely data analytical using standard computer software • setting will be routine settings, with no exposure of other individuals into these settings.
10. Plan for mitigating risk (for researcher and participant safety) a. Participants b. Procedures c. Settings	Research and information governance guidance will be adhered to throughout.

Trainee signature: Date: 22/04/2021

University Supervisor signature: Date: 30/03/21

Appendix 4: PLAIN ENGLISH SUMMARY

Title: How is the prediction of dementia using cognitive scores affected by comorbid pain?

Background

When investigating possible dementia clinical staff often rely on a type of tool called a cognitive screen, which measures mental abilities such as concentration and memory. However we know that factors besides dementia can affect these abilities, including pain (Moriarty et al., 2011). It is possible that people experiencing pain are misidentified as having dementia, because their score is low and falls below a cut-off. Living with pain could also have variable effects which make it harder to draw any conclusions from a cognitive measure. These possibilities have not been formally investigated. This study plans to do so using the UK Biobank, a large existing dataset which contains information on dementia, pain and cognitive performance.

Aims and questions

We want to understand whether identifying dementia using cognitive performance scores becomes harder if people are experiencing pain during the period they completed the measures.

This requires firstly establishing that the cognitive measure has some ability to identify a later dementia diagnosis, and finding the cut-off that is best at separating those who will get dementia from those who do not.

To understand the role of pain, the study will investigate whether people with pain are more likely to falsely be identified as having dementia. It will also determine the strength of the link between cognitive score and later diagnosis, both for people without pain, and those experiencing pain.

Methods

The study will use participants from the UK Biobank. It will compare cases who have developed dementia up to four years after completing the cognitive tests to participants who did not do so, but are similar in key ways (e.g. age, sex, education). We anticipate around 1,000 dementia cases will be involved, with three controls per case.

Recruitment: no new recruitment is needed, originally participants attended assessment centres to get involved.

Consent: this has been completed for all participants as part of the UK Biobank project, who regularly monitor and update the dataset for people wishing to withdraw.

Design: The study will build models that try to identify dementia diagnosis using cognitive information, and see how these are affected by pain.

Data collection: no new data will be collected in the study.

Ethical issues

Use of UK Biobank data does not require project-specific ethical approval as there is an existing approval from the NHS National Research Ethics service. Participants will not be directly affected by the use of their data in the study, which has been anonymised by UK Biobank. Data will be managed and stored within the Institute of Wellbeing.

Practical Applications and Dissemination

The findings may inform clinical guidelines on how to investigate potential dementia when pain is present.

References

Moriarty, O., McGuire, B. E., & Finn, D. P. (2011). The effect of pain on cognitive function: A review of clinical and preclinical research. *Progress in Neurobiology*, *93*(3), 385–404. https://doi.org/https://doi.org/10.1016/j.pneurobio.2011.01.002

Appendix B3 Supplementary analyses (MRP)

Study inclusions and exclusions

Supplementary Table B1. Summary of inclusions and exclusions at each stage of case identification.

context	n	Female n (%)	Have degree n (%)	Age M (SD)
Raw total	9,304	4280 (46)	1861 (20)	63.61 (5.47)
Lacking degree	352	141 (40)	NA (NA)	64.19 (5.25)
remaining	8,952	4207 (47)	1880 (21)	63.59 (5.47)
Neurological condition	1,451	595 (41)	305 (21)	62.1 (6.47)
remaining	7,501	3600 (48)	1575 (21)	63.87 (5.21)
Lacking relevant visit	6,854	3290 (48)	1439 (21)	63.95 (5.14)
remaining	647	259 (40)	149 (23)	63.06 (5.83)
Lacking visit cognitive data	390	160 (41)	86 (22)	63.54 (5.64)
remaining	257	103 (40)	64 (25)	62.33 (6.04)
Acute pain status at visit	33	15 (45)	7 (21)	59.18 (7.45)
remaining	224	87 (39)	56 (25)	62.79 (5.68)

Age = age at first visit

A: Viable cases

Cases must have an active diagnosis and attend UK Biobank for a relevant visit in prior 48 months. This designates active visit value

id	Status	First diagnosis date	First diagnosis	Last diagnosis	Diagnosis	visit 1 date	visit 2 date	visit 3 date	visit 4 date	active visit
1	case	06/04/2014	AD	...	AD	05/10/2010	06/04/2012	...	...	2
1102	case	01/10/2018	Other	...	Other	17/04/2010	...	...	...	none
52240	case	20/02/02017	Other	VaD	VaD	03/03/2010	...	12/04/2014	01/07/2018	3

B: Matching: subsetting

All participants are assigned to one of four subgroups based on *degree*sex* classification

id	Status	Degree	Sex	Subgroup
1	case	no	male	1
825	control	no	male	1
31468	control	no	male	1
79205	control	no	male	1
110456	control	no	male	1
140112	control	no	male	1
277845	control	no	male	1
301653	control	no	male	1
2	control	yes	male	2
3	control	no	female	3
4	control	no	female	4
5	control	yes	female	4
...				

Controls who share a subgroup with a case are then considered for match eligibility

C: Match eligibility / exclusions

1. Active visit

id	Status	visit 1	visit 2	visit 3	visit 4	active visit
1	case	yes	yes	no	no	2
825	control	yes	yes	no	no	2
31468	control	yes	yes	yes	yes	2
79205	control	yes	yes	no	no	2
110456	control	yes	yes	no	no	2
140112	control	yes	no	yes	no	no match
277845	control	yes	no	yes	yes	no match
301653	control	yes	no	no	no	no match

Controls who attended the active visit of the case are retained and given the value 2 in active visit

Those who did not are removed from consideration for this case

2. Survival

id	Status	active visit dat	Recorded death	Days elapsed from active visit: to first diagnosis	Days elapsed from active visit: to death	Meets survival criteria?
1	case	06/04/2012	NA	730	NA	NA
825	control	17/07/2012	NA	NA	NA	yes
31468	control	01/06/2012	NA	NA	NA	yes
79205	control	26/01/2012	12/08/2019	NA	2754	yes
110456	control	19/11/2012	01/04/2013	NA	132	no

Controls are removed when their survival from their active visit's date was shorter than the case duration from active visit to first diagnosis

3. Age caliper

Controls are removed when their age difference is greater than two years from the case in consideration.

id	Status	Age	Difference	Match
1	case	45	NA	NA
825	control	55	10	no
31468	control	47	2	yes
79205	control	45	0	yes

D. Match algorithm - potential control matches = 134,503

Controls that satisfy this process are duplicated in a new data-set and assigned to a case cluster - in this instance, case_cluster_1

id	Age diff
31468	2
79205	0
111412	1
7450	2
224	0
401562	0
12659	0
55396	0
653	0
... to the 398th	

Controls are ordered to minimise age difference and then by their availability, such that controls only available to a few cases are preferred for matching

id	Age diff	Total controls per case	Control available for n cases
79205	0	398	1
224	0	398	1
401562	0	398	1
12659	0	398	1
55396	0	398	2
653	0	398	2
111412	1	398	3
31468	2	398	3
7450	2	398	3

Controls are matched without replacement - such that if control id:653 is selected for the final cluster with case id:1 they could not also form part of another cluster.

Supplementary Figure 1. Overview of selection process. Note only dummy data provided.

PCA information

Supplementary Table 2. Correlations of tests at each visit.

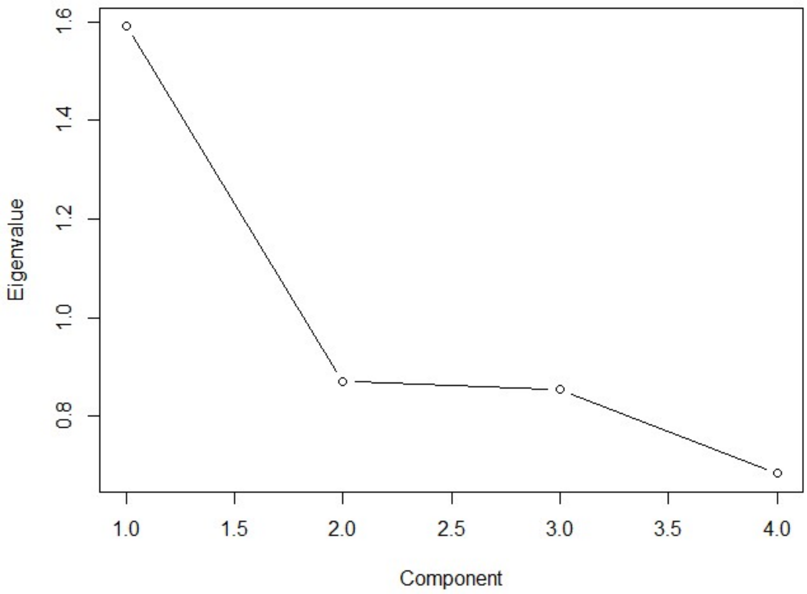
Visit	n at visit	tests	Reaction Time	Visual Memory	Reasoning	Prospective Memory
1	163,706	Reaction Time	1.000	0.144	-0.182	-0.153
		Visual Memory	0.144	1.000	-0.194	-0.148
		Reasoning	-0.182	-0.194	1.000	0.307
		Prospective Memory	-0.153	-0.148	0.307	1.000
2	19,967	Reaction Time	1.000	0.123	-0.167	-0.115
		Visual Memory	0.123	1.000	-0.175	-0.111
		Reasoning	-0.167	-0.175	1.000	0.250
		Prospective Memory	-0.115	-0.111	0.250	1.000
3	44,715	Reaction Time	1.000	0.131	-0.170	-0.123
		Visual Memory	0.131	1.000	-0.169	-0.110
		Reasoning	-0.170	-0.169	1.000	0.223
		Prospective Memory	-0.123	-0.110	0.223	1.000
4	4,215	Reaction Time	1.000	0.157	-0.164	-0.103
		Visual Memory	0.157	1.000	-0.162	-0.121
		Reasoning	-0.164	-0.162	1.000	0.177
		Prospective Memory	-0.103	-0.121	0.177	1.000

NB includes transformed scores for RT and Visual Memory.

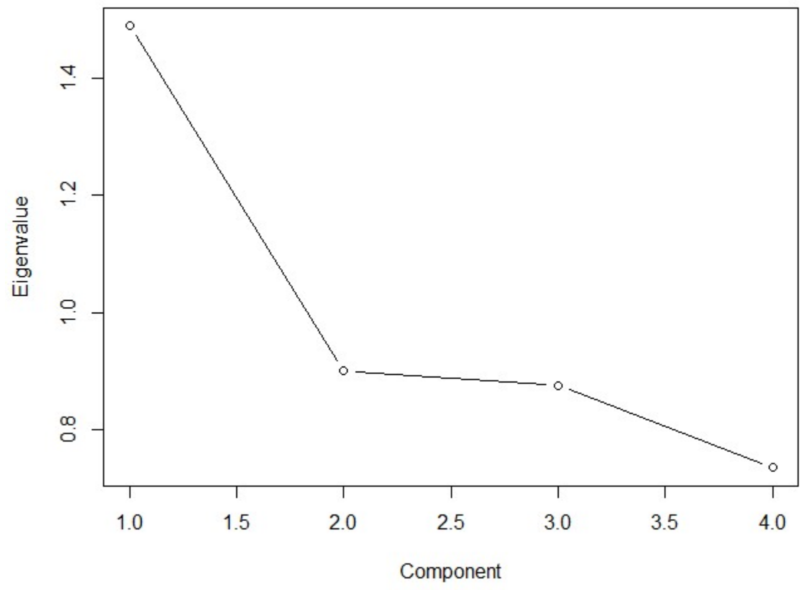
Supplementary Table 3. Factor loadings for each visit

Visit	n at visit	tests	Factor 1	Factor 2	Factor 3	Factor 4
1	163,706	Reaction Time	-0.550	0.552	-0.626	0.031
		Visual Memory	-0.557	0.472	0.677	0.093
		Reasoning	0.717	0.329	-0.015	0.614
		Prospective Memory	0.682	0.485	0.063	-0.544
2	19,967	Reaction Time	-0.541	0.482	0.680	0.113
		Visual Memory	-0.545	0.514	-0.642	0.165
		Reasoning	0.709	0.239	0.036	0.663
		Prospective Memory	0.630	0.589	-0.012	-0.506
3	44,715	Reaction Time	-0.566	0.340	0.739	0.132
		Visual Memory	-0.551	0.599	-0.551	0.182
		Reasoning	0.691	0.214	0.076	0.686
		Prospective Memory	0.609	0.615	0.101	-0.490
4	4,215	Reaction Time	-0.576	0.571	-0.480	0.335
		Visual Memory	-0.603	0.284	0.745	0.015
		Reasoning	0.658	0.171	0.236	0.694
		Prospective Memory	0.561	0.691	0.031	-0.454

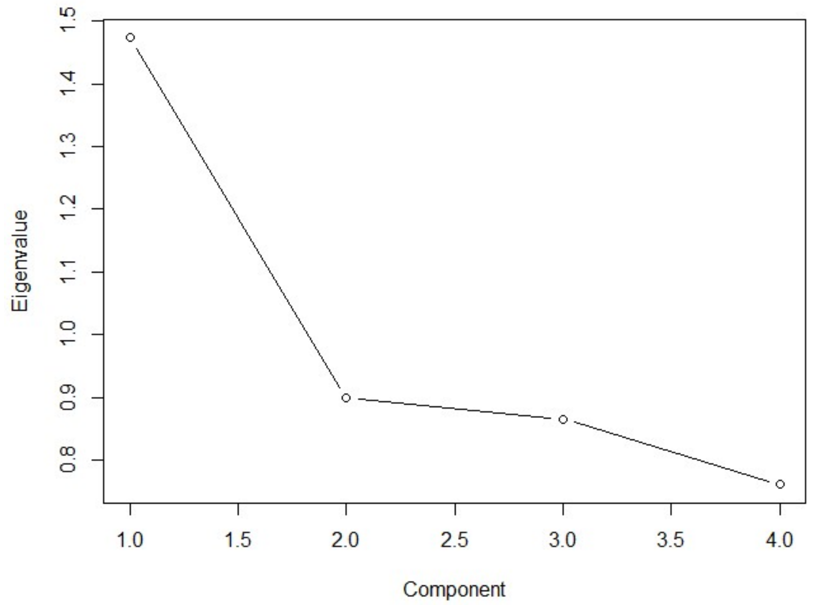
RT scores were significantly positively distributed within the dataset as observed by previous researchers, (e.g. Lyall et al., 2019) so a natural log transform was used to transform this. With the visual memory error scores an LN+1 transformation was taken to account for both the significant skew and the high proportion of zero values. A similar pattern was found by Fawns-Ritchie and Deary (2020) for their dataset.



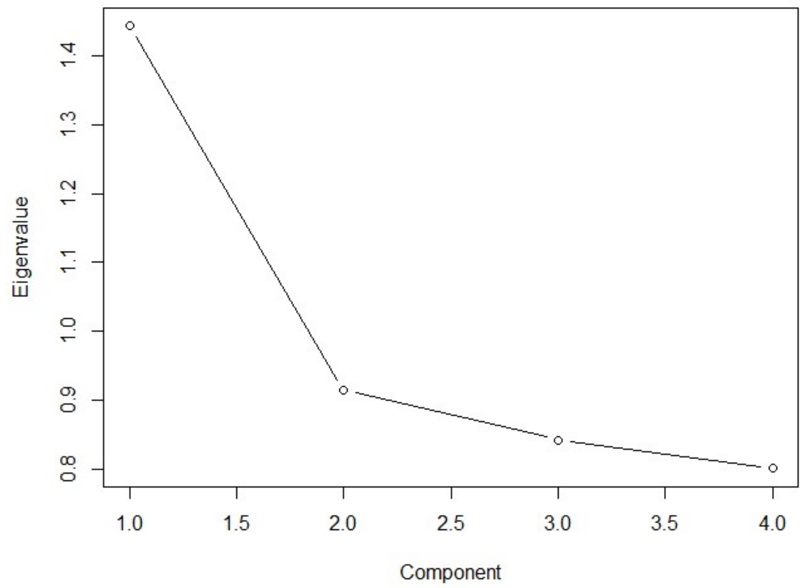
Supplementary Figure 2a. Visit 1 Eigenvalue plot



Supplementary Figure 2b. Visit 2 Eigenvalue plot



Supplementary Figure 2c. Visit 3 Eigenvalue plot



Supplementary Figure 2d. Visit 4 Eigenvalue plot

Sensitivity analysis - pain

We examined the feasibility of running a sensitivity analysis using a pain variable based on the presence of ICD first occurence diagnoses of painful medical conditions. Using lists of pain syndromes from the International Association for the Study of Pain (IASP) (Merskey and Bogduk, 1994, lists 1A, 1F, 1H), the UK Biobank ICD data fields were searched to find these or closest matches to produce a list (see data dictionary linked in Appendix B2). A variable was created for each of the four visits for each patient denoting presence or absence of a diagnosis chronologically prior to that visit date.

In initial exploratory analysis it was found that only 244 of participants self-reporting pain (of 437) also had a diagnosis; more strikingly 163 had a pain-related diagnosis in their health records but reported no pain of any type on the day (of 459 pain-free participants). As a consequence we decided not to run these analyses. The considerations in the discussion on unreliability of health records data may be a feature, together with the fact that the presence of a first occurrence may not reflect the condition being active at the time of the visit. This is particularly so as the lists from the Classification of Chronic Pain are comprehensive and include life-long conditions such as Lupus, more transient ones such as angina, and many intermediate cases, and diagnoses in many instances occurred decades before the active visit.

	Pain Diagnosis	**No condition**
Pain-free	163	296
Chronic	244	193

References

Fawns-Ritchie, C., & Deary, I. J. (2020). Reliability and validity of the UK Biobank cognitive tests. *PloS One*, *15*(4), e0231627. https://doi.org/10.1371/journal.pone.0231627

Lyall, L. M., Cullen, B., Lyall, D. M., Leighton, S. P., Siebert, S., Smith, D. J., & Cavanagh, J. (2019). The associations between self-reported depression, self-reported chronic inflammatory conditions and cognitive abilities in UK biobank. *European Psychiatry*, *60*, 63–70. https://doi.org/10.1016/j.eurpsy.2019.05.007

Merskey, H., & Bogduk, N. (1994). *Classification of chronic pain second edition (revised)*. Seattle: IASP Press.

Appendix B4 MRP Proposal

This link directs to the approved MRP Proposal housed at the OSF site.

https://osf.io/8uvcm