Exploring the Influence of Physical and Mental Health Factors on Older Adults' Performance on the Addenbrooke's Cognitive Examination III (ACE-III)

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Chapter 1: Systematic Review

What is the Impact of Depressed Mood on a Brief Cognitive Screen for Dementia, the Addenbrooke's Cognitive Examination?

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Abstract

Dementia and depression are common clinical presentations in older adult mental health services that can significantly impact quality of life. Overlap in clinical symptoms between depressive disorder and the early stages of a dementia can make differential diagnosis challenging. Brief cognitive assessments are often utilised in memory clinic settings to screen for a possible dementia, or to determine whether more comprehensive neuropsychological assessment is required. The Addenbrooke's Cognitive Examination – third edition (ACE-III) is a widely used cognitive screen for dementia that has been adapted and translated into a number of languages. This current systematic review and meta-analysis aimed to explore the impact of depressed mood on performance on the ACE-III and earlier editions (ACE-R, ACE) in individuals without a dementia. The review followed PRISMA guidelines and studies were assessed for risk of bias using the JBI Critical Appraisal Checklist for Cross-sectional studies. Ten studies with a total of 1882 participants were included in this review. A random-effects meta-analyses was performed, which found an overall medium effect (Hedges' *g* = .66, 95% CI 0.31-1.01) of depressed mood on performance on the ACE. Heterogeneity was high in the analysis (I^2 = 87%). In all comparisons, depressed participants were on average more impaired than controls on the ACE. Variability in the ACE versions and populations utilised across studies in this review may limit the generalisability of findings.

Keywords: Addenbrooke's Cognitive Examination, ACE-III, ACE-R, depression, dementia

Introduction

Dementia and depression are common clinical presentations in older adult mental health services and both can significantly impact quality of life. It is estimated that 55 million people globally have a dementia (WHO, 2020), with a prevalence of 7.1% within the UK population (Wittenberg, 2019). A recent meta-analysis of studies indicated a 13.3% global prevalence of major depressive disorder amongst older adults (Abdoli et al., 2022). In the UK, the prevalence of depressive disorder is suggested to be 7.5%, with the frequency of subthreshold depressive symptoms even more common in the population (De La Torre et al., 2021). Overlap in clinical symptoms between depressive disorder and the earlier stages of a dementia, can make differential diagnosis challenging (Dias et al., 2020). Common symptoms of depression, such as sleep difficulties and apathy, can also be a feature of a dementia (Potter & Steffens, 2007) and concurrently individuals with depression often present with impairment in their cognitive functioning. Cognitive impairment in depression may be more pronounced in the elderly, particularly if the first onset of depressed mood is in late life (Butters et al., 2022). Furthermore depressed mood may be a risk factor for, or a prodrome of, dementia (Bennett & Thomas, 2014) and there is debate within the literature as to the significance of age of onset of depressive symptoms in this association (Byers & Yaffe, 2011). Nevertheless, depressed mood in the absence of a dementing process is a presentation frequently seen in older adult mental health services.

Impaired cognitive functioning in the context of depression has been observed in the form of moderate deficits in the domains of attention, executive function and memory (Rock et al., 2014). Comparatively, the profile of impairment seen in the early stages of Alzheimer's dementia, can be characterised by impaired episodic memory associated with poor consolidation (Bäckman et al., 2001), rapid forgetting, impaired verbal fluency (Rodríguez-Aranda et al., 2016) and dysfunction in the domains of attention (Perry et al., 2000) and executive functioning (Baudic et al., 2006). Comprehensive neuropsychological assessment, utilising a range of different tests that explore functioning across cognitive domains, can differentiate these patterns of impairment. However,

these are often time-consuming to administer and require specialist knowledge for appropriate test selection and interpretation of results. In the first instance, in a memory clinic setting, brief cognitive screens are often utilised to assess for patterns of impairment associated with different profiles of dementia. Screening tools are not diagnostic in and of themselves, but are used in conjunction with collateral history, neuroimaging and clinical assessment to make a diagnosis or determine whether neuropsychological assessment is required.

One such commonly used screening tool is the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh et al., 2013). The ACE-III demonstrates excellent sensitivity (1.0) and good specificity (0.96) for the detection of dementia at a cut-off of 88 and has a lower cut-off of 82 for increased specificity (1.0), but reduced sensitivity (0.93). The ACE-III and earlier versions of this tool, the ACE-R (Mioshi et al., 2006) and the ACE (Mathuranath et al., 2000) are widely used in clinical settings and have been translated and culturally adapted into a number of different languages (Hodges & Larner, 2017). The Addenbrooke's Cognitive Examination is quick to administer and provides subscores in the domains of memory, attention, fluency, language and visuospatial functioning, which can help differentiate the type of dementia. In comparison to another widely used cognitive screen, the Mini-Mental State Examination (MMSE - Folstein, 1983), the ACE is reported to have superior sensitivity for detecting a dementia in its earlier stages and distinguishing between different types of dementia (Mathuranath et al., 2000). However, individuals with depressive symptoms were excluded from patient groups in validation studies of the ACE and previous versions. A study by Blair et al. (2016) exploring the impact of depressive symptoms on the Montreal Cognitive Assessment (MoCA - Nasreddine et al., 2005) found that half the sample of non-demented, depressed individuals scored below cut-off, providing some evidence for the influence of affective symptoms on performance on cognitive screens.

Given that depressed mood is a common mental health presentation in older adults, and that patterns of cognitive impairment may have some overlay with an early dementia presentation, this systematic review will therefore seek to

explore the impact of depressed mood (in individuals without dementia) on the widely used cognitive screen, the Addenbrooke's Cognitive Examination.

Objectives

The aim of this study was to conduct a systematic review and meta-analysis of studies exploring the impact of depressed mood on the Addenbrooke's Cognitive Examination.

Methods

This review adhered to PRISMA guidelines for reporting systematic reviews (2020) and the protocol for this study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [registration number CRD42023423934]. The protocol was amended to clarify that studies would be limited to those published in peer-reviewed journals and to include any single group studies that may have explored an association between exposure and outcome. For the PRISMA Checklist, please see Appendix 1.1.

Eligibility Criteria

This review followed a PECO (Population, Exposure, Comparator, Outcome) structure to identify suitable studies for inclusion. The population (P) of interest were adults (18+) of either sex, with an exposure (E) of depressed mood and a comparator (C) of controls without depressed mood, on performance on the Addenbrooke's Cognitive Examination (O). To maximise the number of eligible papers, all versions of the ACE (ACE, ACE-R & ACE-III) were permitted for this review, including different language versions. Depressed mood was defined by either a clinical diagnosis based on a recognised diagnostic classification system (i.e. DSM or ICD), or a score above cut-off on a validated measure of depression. Studies not meeting these criteria to define their exposure group were excluded.

This review was interested in the performance of individuals with current depressed mood but without a dementia on the ACE-III or earlier versions, in comparison to controls. Therefore exclusion criteria for both the exposure group and the control group of studies was a diagnosis of dementia or any neurological or neurodegenerative condition that is likely to impact on cognitive functioning (for example head injury or stroke). Studies that included participants with a dementia were permitted for inclusion, provided they also had a control group and a depressed mood group without dementia. Comorbid psychiatric disorders (other than a depressive disorder) and substance misuse issues were also excluded from exposure and control groups as these could act as confounds. Cross-sectional studies were the primary focus for this review, however intervention and longitudinal studies could be included provided their baseline data met the above criteria. Studies were limited to those published in English, in peer-reviewed journals. There were no limits to publication date.

Information Sources

Searches were conducted on PROSPERO prior to undertaking this review, to confirm that similar reviews were not in progress. Ovid was used to search the databases EMBASE and MEDLINE and EBSCOhost was used to search PsycINFO and CINAHL. Searches were conducted on the 22nd May 2023.

Search Strategy

Scoping searches were performed to identify relevant papers and key terms before an initial search strategy was piloted in the Medline database. Searches were structured in accordance with the PECO strategy outlined above. Exposure was operationalised using the terms *'depress*' 'affective disorder'* and *'mood disorder'* and outcome defined using *'Addenbrooke*'* and '*ACE-III'* and '*ACE-R'*. These key words were searched for in the main text of articles, to maximise the number of studies. The university librarian was consulted when refining the search strategy for each of the databases used in this review and

selecting relevant subject headings. Full search strategies for each database can be found in Appendix 1.2.

Selection Process

After running searches and removing duplicates, title and abstracts of all extracted studies were screened independently by reviewer 1 (KM) and reviewer 2 (SB) against inclusion/exclusion criteria. Any disagreements in eligibility of studies were resolved by discussion until consensus was reached. Following this, all full texts of studies were reviewed independently by reviewer 1 and reviewer 2 against inclusion/exclusion criteria. Once again, discrepancies on the eligibility of studies were discussed until consensus was reached.

Data Extraction

Data extraction was completed by KM, with 30% of studies reviewed jointly with second reviewer to check accuracy of extraction. The outcome of interest was total scores on the ACE for exposure and control group (mean and standard deviation for groups) and where available, any measure of association between ACE score and a validated measure of depressed mood. Other relevant data extracted were the study characteristics, sample size for groups, participant demographics (in particular age and education level), inclusion/exclusion criteria for groups and the version of the Addenbrooke's Cognitive Examination utilised. Where available and if specified by study authors, cut-offs for the version of ACE used were also extracted or determined by reviewing the index paper for version of ACE included in the study in question. When not specified in the study, literature was reviewed to identify recommended cut-offs for version of ACE used. Study authors were contacted to seek clarity where there was ambiguity regarding the data.

Quality Appraisal

This review was predominantly interested in studies employing a cross-sectional design. Studies included a range of research aims, including those specifically investigating the impact of depressed mood on the ACE or other cognitive screens, and those studies in which the ACE was administered to participants amongst a range of measures and was not a primary focus of the study. Included studies were assessed for quality using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional studies. The JBI Checklist does not produce an overall score, but instead allows each of the 8 items on the checklist to be given a rating of 'yes', 'no', 'unclear' or 'n/a' for each dimension of quality (see Appendix 1.3) . These items are:

1) Criteria for inclusion clearly defined
2) Study subjects and setting described in detail
3) Exposure measured in a valid/reliable way
4) Objective standard criteria used for the measurement of the condition
5) Confounding factors identified
6) Strategies to deal with confounding factors stated
7) Outcomes measures in a valid/reliable way
8) Appropriate statistical analysis used

Some adaptations were made to this checklist to increase relevance for the types of studies that were included in this review, for example the merging of criterion 3 and 4, which for the purposes of this review both concern appropriate definition of depressed mood to classify the exposure group (i.e. use of a recognised classification system, diagnosis made by appropriately qualified clinician). With regards to criterion 5 and 6, particular confounds of relevance were participants' age and education level, which could influence scores on a cognitive screen. Criterion 7 was determined by clear reporting of edition and language version of ACE utilised in study, administration by appropriately trained clinicians and the validation paper for version of ACE used clearly referenced in paper. The exception to this were studies that were validation papers in and of themselves. For this review, criterion 8 was concerned with clear reporting of statistical analyses used to explore outcomes of interest only. Guidance on adaptations to this tool was available to both

reviewers when completing quality appraisal and can be found in Appendix 1.4. Those studies with a higher proportion of 'yes' ratings were considered to be higher quality. Reviewer 1 appraised the quality of all studies according to adapted JBI criteria. Reviewer 2 independently appraised 30% of studies using the same criteria. This resulted in moderate agreement (k = .49) with disagreements between reviewers primarily concerning clarity of reporting within studies. All discrepancies in ratings were discussed until consensus was reached.

Synthesis Methods

The ACE-III and earlier editions (ACE-R and ACE) are all scored out of 100 and all assess the same five cognitive domains (memory, attention, verbal fluency, language and visuospatial skills), however slight modifications to subtests have been made between editions which have resulted in slight differences in weighting for the different domains. Due to different edition and language versions of the ACE cognitive screen used in studies included in this review, a random-effects meta-analysis was performed to calculate standardised mean differences (SMDs) from mean total scores on the ACE for exposure and comparator groups and explore heterogeneity between studies using I^2. Hedges' g was used as the estimated effect size for studies. Meta-analysis was performed using IBM SPSS Statistical Software© - version 29.0.1.0 (171). Subgroup analysis was performed for studies using the same edition of the ACE (ACE, ACE-R or ACE-III) provided at least 3 comparisons were available (even if these incorporated different language versions of the same edition). Study and participant characteristics were summarised in narrative and tabular format, in addition to recommended cut-offs for version of ACE used.

Reporting Bias Assessment

A funnel plot was generated for all studies to explore whether there was any indication of bias in reporting of results. It is noted that for many studies in the analysis, ACE scores were not the primary outcome of interest and therefore bias was considered less likely.

Results

Study Selection

The search process identified 1511 studies. After the removal of 313 duplicates, title and abstracts were screened for 1198 studies according to inclusion/exclusion criteria. A further 1142 were excluded and the resultant full texts of 56 studies were reviewed. Following this, 10 studies met inclusion/exclusion criteria for the study. Backward and forward searches were carried out and a further 5 studies were screened in full text, but did not meet inclusion/exclusion criteria. 1 additional paper was identified that appeared relevant, however the full text was only available in Spanish and therefore could not be included. Therefore the final number of studies included in this review was 10. **Figure 1** provides an overview of this process.

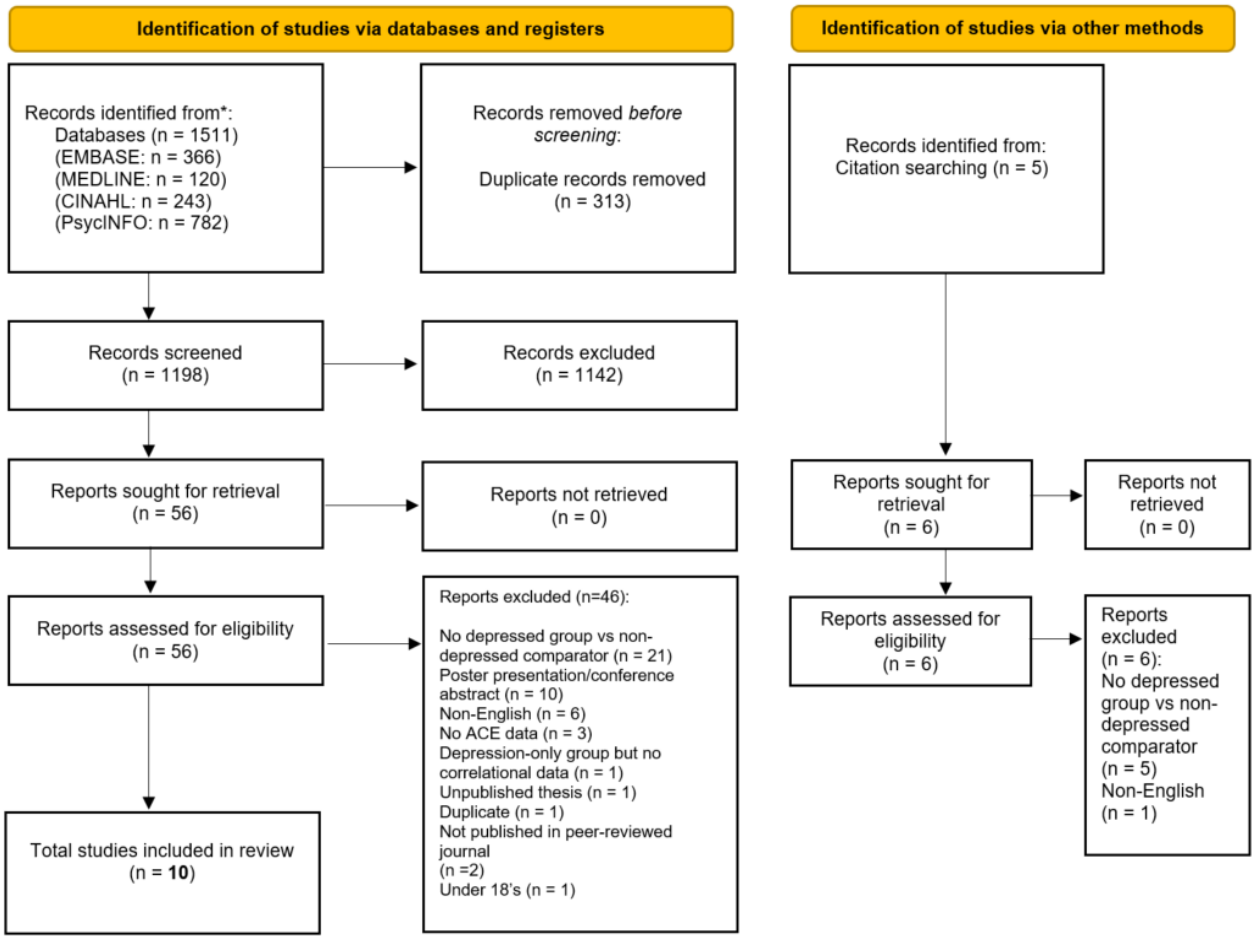

Figure 1 – PRISMA Flowchart

Study Characteristics

Ten studies with a total of 1882 participants were included in this review; 514 with depressed mood and 1368 non-depressed controls. All studies employed a cross-sectional design and included both a depressed mood group and a non-depressed comparator. Half of the studies included in this review (k = 5) reported significantly lower scores on the ACE (or later versions) for the exposure group compared to controls and five studies found no significant difference in performance on the ACE (or later versions) between groups.

For half of the studies in this review, the ACE was the primary outcome measure of interest. These studies either sought to explore differential diagnosis of depressed mood from dementia using the ACE, or validate a non-English language version of the ACE in the respective population. For the remaining five studies, the ACE was administered alongside a battery of other measures including other cognitive tests and influence of depressed mood on the ACE was not key to the research aim.

Studies utilised the ACE (k = 3), the ACE-R (k = 4) and the ACE-III (k = 3). A range of different language versions were included across studies, including five different languages (English, Spanish, Lithuanian, Danish, Portuguese) and three Spanish-language versions, two of which were culturally adapted for different countries (Chile and Peru). For three studies, there was ambiguity around the version of the ACE used and/or language; all of these studies referenced the original English versions of the ACE, but the study locations appeared to be in a non-English speaking country and the first language of participants was not specified. In these cases, study authors were contacted to seek clarification, with one study author responding. No two studies used both the same language and edition of the ACE. **Table 1** summarises the characteristics of studies included.

Sample mean ACE score for depressed groups fell below recommended cut-offs for four of the studies in this review. However, for three of these comparisons, sample mean for the control group also fell below recommended cut-offs for version of ACE used. For two studies, performance of the depressed group relative to recommended cut-offs for dementia screening

could not be determined due to ambiguity about ACE version administered. For a summary of cut-offs for ACE versions utilised in reviewed studies, please see **Table 2**.

Only two studies (Beckert et al., 2016; Rajtar-Zembaty et al., 2022) explored the relationship between ACE scores and a validated measure of depressed mood (Geriatric Depression Scale-Short Form), with neither study finding a significant association between depression severity and ACE performance.

Table 1. Characteristics of Studies

Authors	Country	ACE Edition and Language	Setting	Sample characteristics	Gender Female (%)		Sample Size n	Age Mean (SD)	Years of Education Mean (SD)	ACE Score Mean (SD)	Definition of depression group	Sig
Abdullah et al (2022)	UK	ACE-III (English)	Young onset dementia memory clinic	All younger adults (<66 years) with subjective cognitive complaints. No sig differences between groups in years of education or age	49.4%	Depression	23	59.55 (4.51)	15 (5.68)***	83.26 (11.77)	DSM-V diagnosis of depression	NS
						Control	128	57.78 (6.23)	16.18 (4.43)***	85.63 (11.75)	GDS-4 (supplementary)	
Beckert et al (2016)	Brazil	ACE-R (Portuguese - Brazilian)	Aging Clinic	All low education (<8 years of schooling). 36% of sample illiterate. Depressed group younger.	80.3%	Depression	41	67.5* (6.5)	Unclear	65.95* (10.95)	DSM-IV-TR diagnosis of major depressive episode	NS
						Control	75	70.7* (6.8)		65.93* (11.86)	GDS (supplementary)	
Dudas et al (2005)	UK	ACE (English)	Memory Clinic	No sig differences in age and education level between groups	50.7%	Depression	23	59.1 (7.9)	11.2 (1.7)	89.2 (9.2)	DSM-IV criteria of MDD for MDD group	NS
						Control	127	64.4 (9.4)	11.3 (2.6)	93.9 (3.5)	Ham-D (supplementary)	
Fiorentino et al (2013)	Argentina	ACE-R (Spanish)	Institute of Cognitive Neurology	No sig differences in education level between groups. Depression group significantly younger.	64.3%	Depression	30	60.12 (11.53)	14.17 (3.89)	85.67 (10.88)	DSM-IV criteria for depression	NS
						Control	26	69.23 (8.94)	14.46 (2.23)	95.54 (3.04)		
Herrera-Pérez et al (2013)	Peru	ACE (Spanish - Peruvian)	Neurology clinic	Subjective cognitive complaints in depression group. Depression group significantly younger than controls No sig difference in education level.	49.5%	Depression	21	66* (59-72)**	10* (8-16)**	88* (83-92)**	Beck depression inventory (BDI) - however not clear how cut-offs implemented to define groups	Sig
						Control	70	68* (62-80)**	11* (7-18)**	94* (89-98)**		

***median**
****range**
***** age when left education**

Table 1. – Continued

Authors	Country	ACE Edition and Language	Setting	Sample characteristics	Gender Female (%)		Sample Size n	Age Mean (SD)	Years of Education Mean (SD)	ACE Score Mean (SD)	Definition of depression group	Sig
Jadhav et al (2021)	India	ACE-R (*unclear*)	Psycho-geriatric clinic	91.1% of whole sample were educated. All participants aged 60+. Majority (53.3%) aged 60-65 years	53.3%	Depression Control	30 30	Not specified	Not specified	78.23 (5.84) 78.03 (6.67)	DSM-V criteria for MDD	NS
Ratjar-Zembaty et al (2022)	Poland	ACE-III (*unclear*)	*Unclear*	Sample from previous research study. Did not report or explore education level for groups.	70%	Depression Control	97 613	69.92 (5.29) 69.28 (5.31)	Not specified	90.89 (7.58) 92.56 (5.96)	DSM-V criteria for depression GDS-S (Supplementary)	Sig
Ramos-Henderson et al (2021)	Chile	ACE-III (Spanish - Chilean)	Neuro-psychology Unit / Geriatric Department of Hospital	No sig difference between groups in age and education level	72.5%	Depression Control	102 142	66.35 (9.38) 67.18 (7.96)	9.74 (3.23) 10.05 (3.06)	80.89 (11.77) 84.86 (10.66)	GDS-15. Score ≥5 used to assign to depression group	Sig
Rotomskis et al (2015)	Lithuania	ACE-R (Lithuanian)	Neurology department and mental health clinic	Late-life onset depression group. All participants' ≥4 years of education. Matched for age, years of education and gender	64.5%	Depression Control	117 94	66.33 (8.08) 66.93 (10.26)	11.36 (3.59) 11.93 (2.86)	76.82 (7.36) 85.08 (7.20)	ICD-10-AM criteria for severe depression	Sig
Stokholm et al (2009)	Denmark	ACE (Danish)	Memory clinic	No significant differences between groups in age or education level	*Not reported*	Depression Control	30 63	68 (6.92) 70.33 (6.22)	12.07 (2.94) 12.89 (2.52)	84.80 (9.24) 93.1 (4.55)	ICD-10 criteria	Sig

***median**
****range**
*****age when left education**

Table 2 – Validation data and Cut-offs for ACE Versions used by studies

Author	Country	ACE Edition (Language)	ACE Version referenced by paper	Recommended cut-offs for dementia	Sensitivity/ Specificity	Reliability	Reference for ACE Validation Study		ACE Score Mean (SD)	Average group performance below cut-off	Additional Info from Studies
Abdullah et al (2022)	UK	ACE-III (English)	Yes	88 82	Sensitivity = 1.0 Specificity = 0.96 Sensitivity = 0.93 Specificity = 1.0	Cronbach's α = 0.88	Hsieh et al (2013)	Depression Control	83.26 (11.77) 85.63 (11.75)	Below upper cut off (both groups)	Identified cut-off point of 81.5 to differentiate depressed group from controls (sensitivity = 0.64, specificity = 0.52)
Beckert et al (2016)	Brazil	ACE-R (Portuguese - Brazilian)	Yes	80	Sensitivity = 0.86 Specificity = 0.71	Not available	Amaral-Carvalho et al (2022)	Depression Control	65.95* (10.95) 65.93* (11.86)	Both groups***	
Dudas et al (2005)	UK	ACE (English)	Yes	88 83	Sensitivity = 0.93 Specificity = 0.71 Sensitivity = 0.82 Specificity = 0.96	Cronbach's α = 0.89	Mathuranath et al (2000)	Depression Control	89.2 (9.2) 93.9 (3.5)	No	39% of depressed group scoring below upper cut-off (and 4% of controls) 17% of depressed participants scoring below lower cut-off (0 controls)
Fiorentino et al (2013)	Argentina	ACE-R (Spanish)	English version referenced – clarification sought from study authors	85	Sensitivity = 0.98 Specificity = 0.89	Cronbach's α = 0.89	Torralva et al (2011)	Depression Control	85.67 (10.88) 95.54 (3.04)	No	
Herrera-Pérez et al (2013)	Peru	ACE (Spanish - Peruvian)	Yes	86	Sensitivity = 1.0 Specificity = 1.0	Not available	Custodio et al (2012)	Depression Control	88* (83-92)** 94* (89-98)**	No	Identified cut-off of 86 to differentiate depressed group from dementia (sensitivity = 0.90, specificity = 1.00)

Median group score on ACE
****Range***
*****Median group performance below cut-off on version of ACE***

Table 2 – Continued

Author	Country	ACE Edition (Language)	ACE Version referenced by paper	Recommended cut-offs for dementia	Sensitivity/ Specificity	Reliability	Reference for ACE Validation Study		ACE Score Mean (SD)	Average group performance below cut-off	Additional Info from Studies
Jadhav et al (2021)	India	ACE-R (unclear)	*Unclear*	-	-	-	-	Depression Control	78.23 (5.84) 78.03 (6.67)	-	-
Ratjar-Zembaty et al (2022)	Poland	ACE-III (Unclear)	*Unclear*	-	-	-	-	Depression Control	90.89 (7.58) 92.56 (5.96)	-	-
Ramos-Henderson et al (2021)	Chile	ACE-III (Spanish - Chilean)	Yes	86	Sensitivity = 0.98 Specificity = 0.82	Cronbach's α = 0.87	Bruno et al (2020)	Depression Control	80.89 (11.77) 84.86 (10.66)	Both groups	-
Rotomskis et al (2015)	Lithuania	ACE-R (Lithuanian)	Yes	74	Sensitivity = 0.91 Specificity = 0.90	Cronbach's α = 0.86	Margevičiūtė et al (2013)	Depression Control	76.82 (7.36) 85.08 (7.20)	No	23.9% of depressed group scored below cut-off, compared to 8.5% of controls.
Stokholm et al (2009)	Denmark	ACE (Danish)	n/a – study is validation paper	86	Sensitivity = 0.99 Specificity = 0.94	Not available	Data from Stokholm et al (2009)	Depression Control	84.80 (9.24) 93.1 (4.55)	Depression group	Depressed individuals reduced specificity of optimum cut-offs for dementia from 0.94 to 0.64

Risk of Bias in Studies

Only 1 out of the 10 studies in this review met all criteria on the JBI Critical Appraisal Checklist for Analytical Cross-Sectional studies (see **Table 3**). The majority of studies (60%) adequately described the study subjects and setting (criterion 2). Three studies did not meet criterion 3 (exposure measured in a valid/reliable way) due to no utilisation of recognised diagnostic classification system to define depressed mood, absence of detail on who gave the diagnosis of depression, or ambiguity regarding use of cut-offs on a mood measure to define exposure group. Three studies did not report and/or control for the influence of relevant confounds of age or education level in analysis of ACE performance for groups (criterion 5-6). Half of included studies did not meet criterion 8, due to unclear or incomplete reporting of statistical analyses performed. For the purposes of this review, studies were deemed lower risk of bias if they satisfied a minimum of 7 out of 8 criteria on the checklist. This resulted in four studies judged to be lower risk of bias.

Table 3 – Quality appraisals for studies using the JBI Checklist

Authors	**Inclusion** **1)**	**Study subjects/setting** **(2)**	**Measurement of Exposure** **(3/4)**	**Identification of confounds** **(5)**	**Strategies to deal with Confounds** **(6)**	**Measurement of Outcome** **(7)**	**Statistical Analysis** **(8)**
Abdullah et al (2022)	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Beckert et al (2016)	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear
Dudas et al (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fiorentino et al (2013)	Yes	No	Yes	Yes	Yes	Unclear	Yes
Herrera-Pérez et al (2013)	Yes	Yes	No	Yes	No	n/a*	Unclear
Jadhav et al (2021)	Unclear	No	Unclear	Unclear	No	Unclear	Unclear
Rajtar-Zembaty et al (2022)	Yes	Unclear	Yes	No	No	Yes	Yes
Ramos-Henderson et al (2021)	Yes	Yes	No	Yes	Yes	Yes	Yes
Rotomskis et al (2015)	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear
Stokholm et al (2009)	Yes	Yes	Yes	Yes	Yes	n/a*	Yes

**purpose of paper in and of itself was to validate non-English language version of ACE in population*

Results of Syntheses

Only one study (Ramos-Henderson et al., 2021) reported an effect size for the exposure of depressed mood on cognitive performance on the ACE (Cohen's *d* = .35). Estimated effect sizes were therefore calculated for all studies for the purpose of conducting the meta-analysis, using mean ACE scores, sample size and standard deviation for all groups. Two studies were excluded from meta-analyses (Beckert et al., 2016; Herrera-Perėz et al., 2013) due to failure to provide both means and SD for groups. A random-effects meta-analysis was performed using the remaining 8 out of 10 studies included in this review, with Hedges' *g* as the measure of effect size due to unequal sample sizes and variances between groups. Positive effects represented greater impairment for depressed groups in total score on the ACE cognitive screen. Overall effect size for this meta-analysis was *g* = .66 which indicates a medium effect for exposure of depressed mood on performance on the ACE.

95% confidence intervals for the pooled effect size were broad, ranging from 0.18 - 1.01. Variance in effect sizes between studies was assessed by I^2 which was 87%, indicating high heterogeneity between studies (Higgins et al., 2003). **Figure 2** contains the Forest Plot for this analysis.

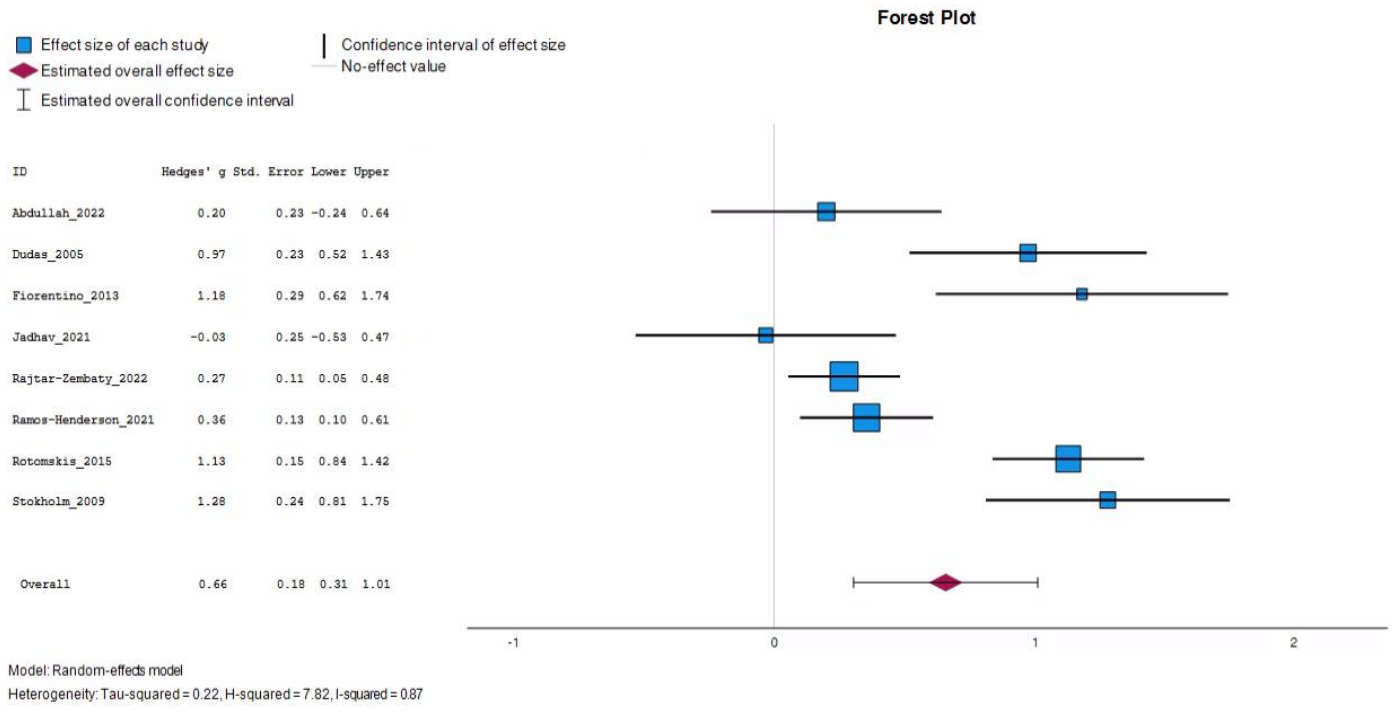

Figure 2 – Forest Plot of effect sizes for studies for exposure of depressed mood on ACE cognitive screen

Subgroup and Sensitivity Analyses

A sensitivity analysis was performed of studies that were assessed to be lower risk of bias in accordance with quality appraisals. This produced comparable effect sizes, confidence intervals and heterogeneity estimates to the meta-analysis of all studies (Hedges' *g* = .69, 95% CI = 0.19-1.18, I^2 = 84%). To explore any variation in effect size estimates across different editions of the ACE and language versions, subgroup analyses were performed on comparisons where at least three studies used the same edition of the ACE (although these comparisons did include different language versions), using random-effects meta-analyses. Results of these analyses can be found in **Table 4** below. All analyses were also performed using Cohen's *d* as the measure of effect size, which produced similar results.

Table 4 – Random-effects meta-analyses for whole sample and subgroups

Group	No of studies	No of participants	Hedges' *g* [95% Confidence Interval]	*p* value	I^2	Studies included
Whole Group	8	1675	0.66 [0.18 -1.01]	<.001	.87	Abdullah et al (2022), Dudas et al (2005), Fiorentino et al (2013), Jadhav et al (2021), Ratjar-Zembaty (2022), Ramos-Henderson (2021), Rotomskis et al (2015), Stokholm et al (2009)
Low risk studies	4	638	0.69 [0.19 - 1.18]	.006	.84	Abdullah et al (2022), Dudas et al (2005), Ramos-Henderson et al (2021), Stokholm et al (2009)
ACE-III	3	1105	.29 [0.14 - 0.45]	<.001	.00	Abdullah et al (2022), Ratjar-Zembaty et al (2022), Ramos-Henderson et al (2021)
ACE-R	3	327	0.77 [0.00 -1.55)	.050	.89	Fiorentino et al (2013), Jadhav et al (2021), Rotomskis et al (2015)

Reporting Biases

Studies in this review included a range of research aims, including those papers for which impact of depressive symptoms on the ACE cognitive screen was a key focus and those for which the ACE was administered amongst a range of other measures. A funnel plot was calculated for all studies included in meta-analyses (see **Figure 3**). The distribution of effects is broadly symmetrical and indicates a low risk of reporting bias amongst included studies.

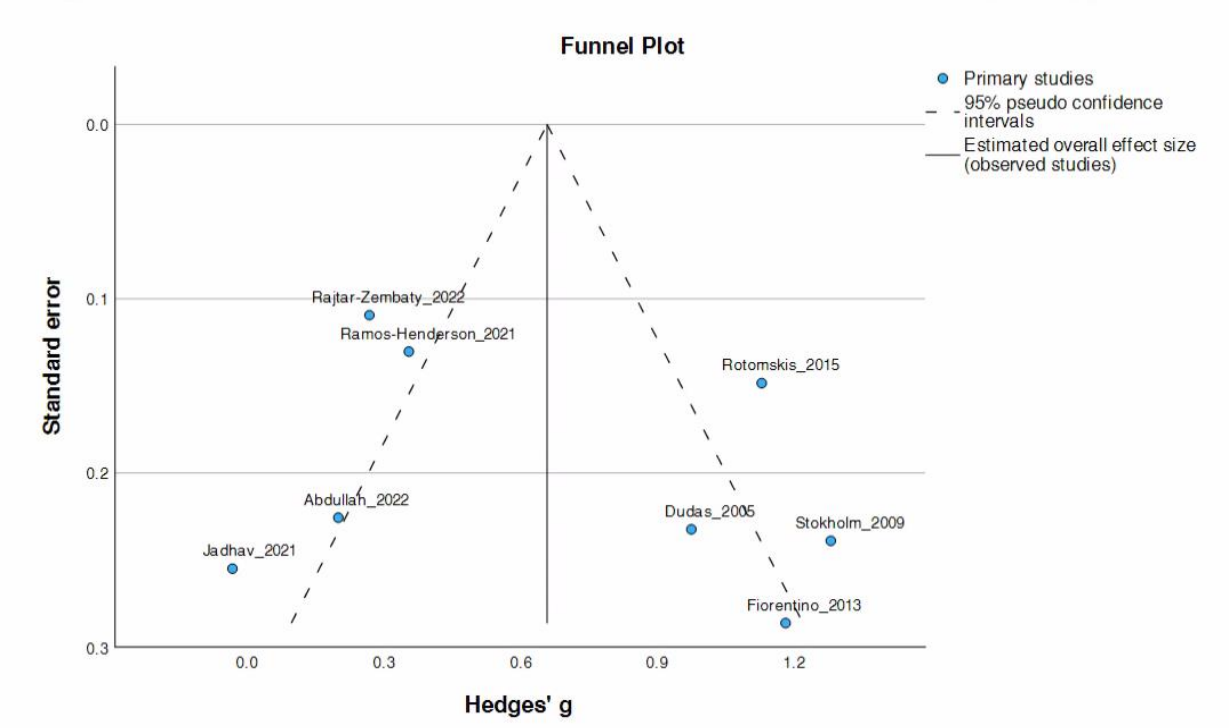

Figure 3 – Funnel Plot

Discussion

This systematic review and meta-analysis explored the impact of depressed mood on performance on the Addenbrooke's Cognitive Examination. Meta-analysis of 8 studies identified an overall estimated medium effect size (*g* = .66) for the exposure of depressed mood on ACE performance. A comparable effect size was found in a sensitivity analysis of those studies considered to be lower risk of bias. However, heterogeneity between studies was high and wide confidence intervals were observed across all analyses, indicating a lack of precision in estimates of effect size. For those studies that utilised the ACE-III specifically, a smaller estimated effect size was observed (*g* = .29) but with narrower confidence intervals. However this analysis included only three studies, with different languages, and so generalisability is limited. Study quality did not appear to be associated with study results, as both high and low quality studies reported significant and non-significant differences between groups in the outcome of interest. Furthermore, significant findings across

studies in this review were not differentiated by failure to control for the potential confounds of age and years of education.

Although statistically significant differences in ACE performance were only found in half of the studies in this review, all studies reported lower overall ACE scores for the depressed group in comparisons to controls. For some studies, large, although not statistically significant, differences in ACE scores across groups could be attributed to small sample sizes and reduced power (e.g. Fiorentino et al., 2013). Comparatively, some of the studies reviewed that employed larger samples, found statistically significant differences with much smaller decrements in overall ACE score for depressed individuals (e.g. Rajtar-Zembaty et al., 2022). Of the studies that provided this data, one study found that the proportion of depressed individuals scoring below recommended cut-offs for dementia screening on the ACE was 39% (below the upper cut-off), compared to 4% of controls and 17% (below the lower cut-off), compared to 0% of controls. Another study found that 23.9% of their depressed sample fell below the single recommended cut-off for this version of the ACE, compared to 8.5% of their control group.

Furthermore, in studies utilising ROC analyses, reductions in specificity at established cut-offs for identifying possible dementia were observed following the inclusion of non-demented individuals with depressed mood in the sample. The findings of this review indicate that there may be an increased risk of dementia misclassification for individuals with depressed mood, as assessed by the ACE (and later versions). However, the Addenbrooke's Cognitive Examination may be less sensitive to cognitive impairment related to depression than the MoCA cognitive screen, where comparatively a previous study found that 50% of their sample of depressed individuals without dementia scored below cut-off (Blair et al., 2016).

Domain-specific impairments in ACE performances were observed for individuals with depressive symptoms relative to controls in three of the included studies in this review (Dudas et al., 2005; Rotomskis et al., 2015; Jadhav et al., 2021), relating to impairments in memory, fluency and visuospatial functioning. However, two further studies (Beckert et al., 2016;

Abdullah et al., 2022) in this review found no significant differences between depressed and non-depressed individuals across domains as assessed by versions of the ACE. One of these studies included a low education sample, 31% of whom were illiterate, which likely impeded performance on ACE subtests requiring reading and writing. Indeed mean ACE scores for this sample were the lowest out of all studies included in this review (65.95 for the depressed group, 65.93 for the control) highlighting the potential for education level to impact scores on this screen. At odds with previous research (e.g. Rock et al., 2014), no studies included in this review found poorer performance from individuals with depression on tasks of attention. Such impairments may be less evident on a brief cognitive screen, in comparison to a more comprehensive battery of tests, although attentional dysfunction in depressed but not demented individuals has been observed through assessment of cognitive functioning using the MOCA brief screen (Blair et al., 2016).

Limitations of the Evidence & Review Process

This review included studies that incorporated a range of different editions and language versions of the Addenbrooke's Cognitive Examination. Included studies were conducted in a broad range of countries and cultural contexts with diverse populations, which may account for the heterogeneity in effect sizes observed between studies.

Although the different editions of the ACE (ACE-R, ACE-III) are very similar, the inclusion of different language versions in this review introduced additional variability between measures, which may further limit the ability of this review to draw comparisons between studies. Furthermore, even within same-language versions of the ACE, additional adaptations are often made for specific countries and cultures, for example augmentation of items in picture naming tasks to increase cultural relevance. If the adaptation process is not robust, and the adapted version is not properly piloted and then validated in the target population, the accuracy of the ACE as a screening tool may be reduced. In line with this, a systematic review by Habib and Stott (2019) explored the diagnostic accuracy of non-English adaptations of the ACE and found that,

despite studies reporting excellent accuracy, cut-offs for different language and same language versions of the ACE varied for classification of dementia. This was also observed in the process of reviewing literature for this systematic review, which in some instances identified multiple validation papers for the same language-version and edition of the ACE, all stipulating different optimum cut-offs for the screening of a dementia. In one instance, the referenced validation paper reported perfect sensitivity (1.0) and specificity (1.0) for specified cut-offs to differentiate patients with dementia from healthy controls.

In addition to cultural differences in study populations in this review, included studies also varied in terms of sample characteristics and their source of participants for the control group. Amongst those studies reporting significant differences in ACE scores between depressed and non-depressed groups, control groups were composed of 'healthy volunteers' from community populations, or spouses of patients attending clinics. In contrast, the control groups for those studies reporting non-significant results were much more varied, with some studies recruiting controls from clinical populations (for example, a memory clinic), or in some cases not sufficiently describing the characteristics of the control sample.

This distinction in status of control group can be observed in the Funnel Plot, which depicts two distinct clusters of effect sizes. Those studies utilising a non-clinical healthy control sample are clustered to the right of the plot demonstrating larger effect sizes for the influence of depressed mood on ACE performance, compared to those studies clustered to the left of the plot, who either recruited control participants from a clinical population, or did not sufficiently describe the origins of the control sample. Although all studies excluded dementia in both control and depressed mood groups, complexity and comorbidities often seen in clinical populations may have confounded any impact of depressed mood. This may explain the finding for some studies in this review of below cut-off average performances on the ACE for both the depressed and control groups. However it should be noted that all studies included in this review reported large standard deviations for mean ACE performance across groups, demonstrating a wide variation in scores for non-demented participants with and without depressed mood.

This review included higher and lower risk of bias studies of a range of methodological quality, with only one study meeting every criterion on the quality appraisal tool. Failure by some studies to either control for or explore the influence of age and education level of participants, may have reduced ability to detect any influence of depressed mood on the Addenbrooke's Cognitive Examination, although significant and non-significant results were not differentiated by this factor. Incomplete reporting of version and edition of ACE utilised by studies made it challenging to draw comprehensive comparisons for all studies included in this review. Another relevant factor that was not reported by studies in this review, was the antidepressant medication status of participants, which could influence cognitive functioning in depressed individuals.

Conclusions and Implications

This systematic review found overall small decrements in ACE performance for non-demented individuals with depressed mood compared to those without. However, heterogeneity across samples in this review was high and a broad range of ACE scores were observed for participants with depressed mood, within and between studies. Whilst this finding could be partially attributed to the diversity of participants, cultural contexts and methodologies that studies utilised, this variation in performance on a brief cognitive screen may also indicate that individuals with depressed mood are differentially impaired in their cognitive functioning. This finding highlights the importance of screening for mood difficulties as part of any dementia assessment process and being cautious in the interpretation of scores from cognitive screening tools such as the Addenbrooke's Cognitive Examination, in people with depression.

Statement and Declarations

The author has no competing interests to declare

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Chapter 2: MAJOR RESEARCH PROJECT

Exploring the Influence of Physical and Mental Health Factors on Older Adults' Performance on the Addenbrooke's Cognitive Examination III (ACE-III)

Prepared in accordance with the author requirements for the journal Applied Neuropsychology: Adult

Submit to Applied Neuropsychology: Adult (tandfonline.com)

Plain Language Summary

Title

Exploring the Influence of Physical and Mental Health Factors on Older Adults' Performance on the Addenbrooke's Cognitive Examination III (ACE-III)

Background

When investigating whether someone may have dementia, clinicians often use short assessment tools called cognitive screening tests, which look at thinking abilities including memory and language. One commonly used screening test is the Addenbrooke's Cognitive Examination III (ACE III – Hsieh et al., 2013). An overall score on this test below a certain value suggests that the person may have a dementia, and so ACE-III results are often used, alongside other information, to make a diagnosis of dementia or to decide whether more detailed tests of cognitive abilities are needed.

Sometimes people who complete the ACE-III get a low score on the test but do not get a diagnosis of dementia, after all the relevant information about that person is put together and reviewed by clinicians. In these cases, there are lots of other factors that could be affecting performance, including physical health and mental health conditions that are common in older adults and their level of intellectual functioning before the onset of any disease.

Aims

This study aimed to explore whether different physical and mental health factors have a negative impact on older adults' performance on the ACE-III, and if so, by how much.

Methods

Research was reviewed to identify common physical and mental health conditions in older adults that may influence cognitive functioning. Participants were individuals who received an assessment of their memory in a community

mental health service for older adults. Electronic clinical notes were reviewed to identify those that did not get a dementia diagnosis following an assessment of their thinking abilities, to look at the influence of a range of physical health, mental health and demographic factors on participants' scores on the ACE-III.

Results

None of the physical health and mental health factors looked at in the study were associated with scores on the ACE-III. The only factor that was associated with ACE III performance was a measure that estimates intellectual ability. The majority of participants, despite not receiving a diagnosis of dementia at the point of assessment, scored below cut-off used to indicate cognitive difficulties on the ACE-III.

Conclusions

Patients assessed in memory clinics often present with complex co-morbid chronic physical and mental health conditions and may often score below cut-off on the ACE-III despite not meeting criteria for a diagnosis of dementia. Although a useful screening measure, the ACE-III should be used alongside other sources of information including clinical history and report from a significant other, as part of the screening process. Developing adjusted cut-offs for the ACE-III according to patient's education level, may improve its accuracy as a screening tool.

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Word count: 485

Abstract

The ACE-III is a widely used cognitive screen for dementia. This retrospective study aimed to explore the potential influence of common chronic physical health and mental health conditions in an older adult population on total score on the ACE-III, as well as influence of premorbid intellectual functioning, using existing clinical data. Participants were 135 memory clinic patients assessed using the ACE-III and not given a diagnosis of dementia following neuropsychological assessment. Regression analyses were performed to explore influence of physical and mental health variables on total scores on the ACE-III. The only significant predictor of variance in ACE-III score was premorbid IQ, which demonstrated a weak positive correlation (r = .39). No other physical and mental health variables significantly predicted scores. The majority of the sample scored below cut-off on the ACE-III, despite not meeting criteria for a diagnosis of dementia at the time of assessment. Prevalence of physical and mental health conditions was high in this memory clinic sample but a statistical relationship between exposure to these conditions and ACE-III performance was not detected. Although a useful screening measure, the ACE-III should be used alongside other sources of information including clinical history and reports from a significant other, as part of a screening process. Development of adjusted cut-offs for the ACE-III according to patient's education level, may improve its accuracy as a screening tool.

Keywords: Addenbrooke's Cognitive Examination, ACE-III, dementia, premorbid IQ

Introduction

Cognitive Screening and Dementia

Cognitive screening tests are an important tool in clinical practice for the detection of cognitive changes which can indicate the emergence of a dementia and inform whether further investigations are required. Early detection of dementia may have a number of benefits including better ability to plan care (Rasmussen & Langerman, 2019) and consideration of pharmacological interventions that may slow progression of Alzheimer's Dementia (Tinklenberg et al., 2007). One commonly used screening tool for dementia is the Addenbrooke's Cognitive Examination III (ACE-III, Hsieh et al., 2013).

The ACE-III has good sensitivity and specificity for identifying dementia (Hsieh et al., 2013) and is sensitive to a broad spectrum of cognitive change including Mild Cognitive Impairment (MCI) and dementia (Matias-Guiu et al., 2016). It provides a total score for cognitive function as well as sub-scores for the domains of language, attention, visuospatial, memory and fluency, with higher scores corresponding to better cognitive function. The ACE-III is routinely used to screen for dementia in clinical services; scores below cut-off, in conjunction with a corroborating clinical history, may be used to make a diagnosis of dementia, or to inform whether further neuropsychological testing is needed on occasions where there is ambiguity. Although the ACE-III is not a substitute for comprehensive neuropsychological assessment and should not be used diagnostically on its own, it is widely utilised to inform dementia assessment. In clinical practice, some patients score below cut-off on the ACE-III but do not go on to get a diagnosis of dementia following neuropsychological assessment. On these occasions, other factors associated with the individual's mental and physical health may be influencing scores.

Impact of Physical Health on Cognitive Function

The UK population is ageing, and it is projected that there will be an additional 7.5 million people aged over 65 in 50 years-time (Office for National Statistics – ONS 2021). However, the number of years spent in good health is declining, resulting in a growing elderly population who are living in ill-health for longer (Welsh et al., 2021). Furthermore, the prevalence of multi-morbidity – multiple co-occurring chronic diseases such as diabetes, cancer, stroke or cardiovascular disease – increases with age (Salisbury et al., 2011). A study of older adults in Scotland estimated that approximately 65% of people aged 65-84 and 82% of people over the age of 85 had multiple chronic health conditions (Barnett et al., 2012). Despite prevalent usage of the term in the literature, there is no universally accepted definition of what constitutes a 'chronic' health condition or disease and definitions make reference to a range of factors such as disease duration, associated functional impairment, communicability and treatability (Goodman et al., 2013). The WHO adopts a more general definition, referring to chronic diseases as those conditions that are "of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors" (World Health Organisation, 2014).

There is evidence to suggest that many of these common chronic health conditions are associated with impairment in cognitive functioning. For example, one study found that individuals with diabetes performed significantly worse on tests of executive function, attention and language ability when compared to controls (Palta et al., 2017). In addition, Chronic Obstructive Pulmonary Disease (COPD), has been identified as a major risk factor for cognitive impairment due to the hypoxemia caused by the condition (Thakur et al., 2010). Furthermore, chronic pain, another common presentation in the elderly, is associated with impairments in general cognitive functioning as well as deficits in the domains of attention and executive functioning (Moriarty et al., 2011). Of particular current relevance, there is growing research on the impact of Covid-19 on cognitive abilities. A study by Hampshire et al. (2021) found that individuals who have recovered from Covid-19 exhibited significant cognitive deficits when compared to controls, particularly in executive functioning performance. This was despite the study controlling for pre-existing

medical conditions, and the sample including a range of symptom severity, including those who did not receive any medical attention for the condition (Hampshire et al., 2021).

Due to experiencing an elevated number of comorbid chronic health conditions, older adults are commonly on multiple medications; so-called 'polypharmacy' (Hajjar et al., 2007). One broad category of medications, frequently prescribed to older adults, are drugs that have an anticholinergic effect. This category spans many groups of psychotropic and non-psychotropic medications including antihistamines, benzodiazepines, some antidepressants, barbiturates and muscle relaxants. These are used to treat a myriad of physical and mental health conditions, and act by binding to receptors and blocking acetylcholine neurotransmission, which can have adverse effects on central nervous system function (López-Álvarez et al., 2019). The use of anticholinergics in England's older population has increased, and the prevalence of the most potent anticholinergics almost doubled from 5.7% in 1990-1993 to 9.9% in 2008-2011 (Grossi et al., 2020). A systematic review of 46 studies including over 60,944 participants found a significant decline in cognitive ability with increasing anticholinergic load, indicating a dose-response relationship (Fox et al., 2014). Exposure to anticholinergic medication may therefore be an important factor to consider when investigating older adults' cognitive performance.

Many of the risk factors for the emergence of late-life cognitive impairment may be modifiable. A comprehensive report and evidence review by the Lancet Commission (Livingston et al., 2020) identified 12 risk factors that are estimated to account for up to 40% of dementia occurrence globally. These are: low education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury and air pollution. The report highlights the importance of identification of potentially modifiable risk factors for dementia, which may potentially be mitigated with appropriate social, environmental and lifestyle intervention.

Impact of Mental Health on Cognitive Function

In addition to physical health status, there is considerable research exploring the impact of common mental health presentations on an individual's cognitive functioning. Individuals with depression assessed using a battery of neuropsychological tests demonstrate cognitive impairment, not just during active episodes of depression, but also during periods of remission (Rock et al., 2013). Major depression can have a negative impact on episodic memory, executive functioning and processing speed (McDermott & Ebmeier, 2009). There is also evidence to suggest that presence of an anxiety disorder may negatively impact cognitive functioning. A study by Airaksinen et al. (2005) found that individuals with Panic Disorder and Obsessive-Compulsive Disorder demonstrated poorer performance on tests of episodic memory and executive functioning in comparison to controls. Another study found that older adults with Generalised Anxiety Disorder demonstrated impairments in their short-term memory compared to non-anxious controls (Mantella et al., 2007).

While research examining the impact of a range of physical and mental health conditions on cognition exists for neuropsychological tests, there are a lack of studies investigating the impact of such factors on cognitive screens. Terpening et al., (2010) examined the characteristics of patients scoring below cut off who did not have a diagnosis of dementia on an earlier version of the Addenbrooke's, the ACE-R (Mioshi et al., 2006), and found that patients in the false positive group typically had a prior history of stroke, significant cerebrovascular disease, a high number of medical comorbidities and polypharmacy. Furthermore, a study investigating the impact of chronic pain on performance on another brief cognitive screen, the Montreal Cognitive Assessment (MoCA, Nasreddine et al., 2005) found that individuals in the chronic pain group performed significantly worse on this test (Ferreira et al., 2016). Comparatively, there is sparse literature looking at what factors other than dementia may be impacting on ACE-III scores.

Premorbid Functioning and Cognitive Screening Tests

Tests of premorbid ability are a common component of neuropsychological assessments, used to generate a baseline against which to compare current cognitive performance. Expectations of performance on neuropsychological testing can be adjusted according to this estimate of premorbid ability, and the discrepancy between expected and achieved scores used to inform a probable diagnosis of dementia or mild cognitive impairment. However, premorbid intellectual functioning is not taken into consideration when scoring a brief cognitive screen such as the ACE-III, despite being a determinant of cognitive performance. A study by Stott et al. (2017) examined the impact of premorbid IQ as assessed by the TOPF (Test of Premorbid Functioning – Wechsler, 2009), on performance on the ACE-III. Premorbid IQ and ACE-III performance were found to be highly associated, but the authors did not find any improvement in screening accuracy for dementia when accounting for premorbid IQ. However, the control sample for this study was of above-average premorbid IQ, making it difficult to draw conclusions about the possible impact of lower premorbid functioning on ACE-III performance.

Alves et al. (2013) looked at the influence of premorbid IQ on two other brief cognitive screens; the MoCA and the Mini-Mental State Examination (MMSE – Folstein et al., 1975) and found that premorbid IQ predicted between 8.4-33.2% of variance on these screening tests. Given its potential impact on measures of cognitive performance, the current study will also examine the influence of premorbid IQ, as assessed by the Test of Premorbid Functioning (Wechsler, 2009) on ACE-III scores. Multiple reading tests exist for the assessment of crystallised intelligence, which are suggested to be robust to the impairment associated with a dementia. The TOPF is widely used due to the test having been co-normed with the 'gold standard' assessment for intellectual functioning, the Wechsler Adult Intelligence Scale (WAIS-IV – Wechsler et al, 2008). It requires the individual read out a list of 70 phonetically irregular words, with a point awarded for every word correctly pronounced. Points are summed to generate a raw score, which can be adjusted according to demographics to generate an estimate of premorbid intellectual functioning, corresponding to the WAIS-IV.

Impact of Alcohol & Sleep on Cognition Function

Ageing is associated with changes in sleep patterns, with older adults typically experiencing more fragmented sleep that is shorter in duration and poorer in quality (Yaffe et al., 2014). These changes can be attributed to a number of factors prevalent in an elderly population, including an increased incidence of certain medical conditions and prescription medications that can interfere with sleep, and sleep disorders (Wolkove et al., 2007). Poor sleep is associated with impaired cognitive functioning, in both healthy older adults and those with underlying conditions, although the exact mechanisms through which this occurs are not known (Dzierzewski et al., 2018). McSorley et al. (2019) found that disrupted sleep as measured by actigraph was associated with lower scores on a brief cognitive screen, the MoCA-SA, a version of the Montreal Cognitive Assessment (Kotwal et al., 2015).

Another important factor that can negatively impact cognitive performance is heavy alcohol consumption. Excessive alcohol intake can cause damage to areas of the brain, in particular to the frontal lobe, and is associated with increased risk of dementia (Kim et al., 2012). A cohort study of over 10,000 older adults in Canada, found that alcohol abuse among older adults was common, particularly amongst men, and is associated with impaired cognitive functioning (Thomas & Rockwood, 2001). Memory and motor functions can be particularly affected, however a history of heavy alcohol consumption, even in the absence of current heavy use, can have negative lasting consequences for overall cognitive functioning, (Woods et al., 2016). Due to the prevalence of sleep difficulties and chronic alcohol consumption in an older adult population, the current study will also seek to examine whether the presence of these factors impacts on performance on the ACE-III. Given the preponderance in older adults of health conditions associated with impaired cognitive functioning, investigating whether these factors have the potential to influence scores on a commonly used cognitive screen, is of clinical value.

Aims & Research Questions

The primary aim of this study is to explore whether the presence of certain physical health and mental health conditions prevalent in an older adult population have an influence on performance on a widely used brief cognitive screen, the ACE-III. The study aimed to examine this through retrospective analysis of existing data from a sample of patients who were referred to an Older Adult Community Mental Health Team for neuropsychological assessment following a query of cognitive impairment, but were not given a diagnosis of dementia.

Specifically, the study examined the relationship between ACE-III scores in this sample and the presence of:

1. Chronic Health Conditions
2. Pain
3. Psychiatric Disorders
4. Anticholinergic Medication
5. Alcohol/Substance Misuse
6. Sleep Difficulties

Furthermore, the study explored the possible influence of premorbid functioning, as captured by the Test of Premorbid Functioning (TOPF) on ACE-III scores.

This was explored through the following research questions:

1. Can variance in ACE-III scores be explained by:

i. Presence of a Chronic Health Condition
ii. Presence of Pain
iii. Presence of a Psychiatric Disorder
iv. Exposure to Anticholinergic Medication
v. Alcohol/Substance Misuse difficulties
vi. Sleep Difficulties

vii. Level of Premorbid Functioning

And if so, by how much?

2. Which, if any, of these variables is the best predictor of ACE-III score?

3. Is there an additive effect of:

i. Chronic Health Conditions
ii. Mental Health Conditions

Methods

Participants

Participants were adults referred to older adult community mental health teams in NHS Greater Glasgow & Clyde (NHS GG&C) due to complaints of cognitive impairment. All participants had an ACE-III administered by a psychiatrist, clinical psychologist or community psychiatric nurse and had also completed a neuropsychological assessment. Only participants who did not go on to get a diagnosis of dementia within 12 months of assessment were included in this study. This group were of interest as dementia is less likely to have contributed towards their ACE-III score and so the potential influence of other health factors on cognitive functioning could be explored. This study was limited to those who completed a neuropsychological assessment as data pertaining to variables of interest (i.e. psychometric measures of mood, premorbid functioning) are systematically collected during this assessment, reducing the chances of missing data.

Eligibility Criteria

<u>Inclusion</u>

To be eligible for inclusion, participants needed to have completed an ACE-III and neuropsychological assessment within six months of each other. Suitable cases were those that had the ACE-III administered in its entirety, with a total score reported for this measure and the date of administration documented. Only participants who did not receive a diagnosis of dementia by a psychiatrist within 12 months of neuropsychological assessment were included.

Exclusion

Participants were excluded from the sample if they had a) more than 6 months between administration of the ACE-III and neuropsychological assessment b) a diagnosis of dementia given by a psychiatrist within 12 months of neuropsychological assessment c) an existing diagnosis of any neurological condition that is likely to significantly impair cognition (e.g. epilepsy, stroke, Parkinson's Disease).

Dataset

The source of data were electronic patient records stored on the software EMIS (Older Adult Community Mental Health Team records) and Portal (patient medical records) in a single health board in Scotland. Following ethical approval, all older adults marked on the system as having had a neuropsychological assessment were located through retrieval of their unique patient identifier numbers (CHI numbers). This information is routinely recorded using a template applied to collect data on Local Delivery Plan (LDP) Standards for the Scottish Government. To account for any individuals who may not have been marked on the system as having had a neuropsychological assessment, an email request was also sent to Clinical Psychologists working in Older Adults Community Mental Health Teams across the health board, asking if they could identify any neuropsychological assessments they had completed in the last four years with patients who were not diagnosed with dementia following this assessment. The two lists were combined and cross-referenced to remove any duplicate patients. Clinical notes for all participants identified were reviewed to access information on patient demographics, pre-

morbid intellectual functioning, physical health and mental-health related factors. Data were extracted for variables of interest in accordance with the coding protocol developed.

Variables of Interest & Coding

A review of epidemiological research was conducted to identify the most prevalent physical health and mental health conditions in an older adult population in the country of origin of the study. From this review, a list of nine chronic health conditions and three categories of psychiatric conditions were created, in addition to five other variables of interest; presence of pain, anticholinergic medication, alcohol/substance misuse, sleep difficulties and premorbid functioning. Dichotomous variables were created for all health variables (present/absent) for each participant. Continuous variables were total ACE-III score (dependent variable) and age as a covariate. Raw scores on the test of premorbid functioning (TOPF) were planned to be included in the analysis as a continuous variable, however data were not routinely available in clinical notes. Instead, range estimates of premorbid intellectual functioning for participants (extremely low, borderline, low average, average, high average, superior and very superior) generated by the TOPF and documented on neuropsychological assessment reports, were collated and coded as an ordinal variable. Demographic data (age, sex) and data for variables of interest were extracted for each participant from clinical notes and collated for analysis. For further information on prevalence data for variables of interest and the coding protocol developed for these variables, please see Appendices 2.1-2.6.

Design

The study employed a cross-sectional observational design to retrospectively analyse clinical health data gathered routinely for patients attending older adult community mental health teams for assessment of their cognitive functioning. Relevant data was extracted from electronic clinical records and collated on a password protected Excel spreadsheet, stored securely on the NHS network

drive. Cases were pseudonymised and given a randomly-generated four-digit ID, with the list of patient names and CHI numbers stored separately in a password protected document.

Measures

Total score on the ACE-III brief cognitive screen was the outcome variable of interest for this study. The ACE-III is scored out of 100, and has two cut-offs, 88 and 82, which differentially prioritise sensitivity and specificity. At a cut-off of 88, sensitivity is reported to be 1.0, specificity 0.96. At a cut-off of 82, sensitivity is reported to be 0.93, specificity is 1.0. Scores below these cut-offs are suggestive of a possible dementia.

Analysis Plan

This study aimed to answer the research questions through a series of regression analyses, to explore any relationship between ACE-III score and health variables, predictive power of variables and any possible additive effect of presence of multiple physical and mental health conditions on ACE-III score. Data were analysed using the statistics package IBM SPSS© - version 29.0.1.0 (171)

Due to the large number of predictor variables, the first stage of analysis consisted of a series of univariate linear regressions performed for each of the 17 predictor variables (see **Table 5**) to examine whether any of these were significantly associated with total score on the ACE-III.

Table 5 – List of Predictor Variables for Initial Analysis

Predictor Variable	No. of Variables within Category
Chronic Health condition **Type 2 Diabetes** **Chronic Kidney Disease** **Chronic Heart Disease** **Autoimmune Disorder** **COPD** **Osteoarthritis** **Covid-19** **Cancer** **Hypothyroidism**	9
Chronic Pain	1
Mental Health Condition **Depressive Disorder** **Anxiety Disorder** **Chronic Mental Health Disorder**	3
Anti-Cholinergic Medication	1
Alcohol/Substance Misuse	1
Sleep difficulties	1
Premorbid Functioning	1
Total Number of Predictor Variables = 17	

To answer the second research question, the second stage of analysis planned was hierarchical multiple regression with a reduced number of predictor variables, to explore whether any of these variables made a statistically significant contribution towards unique variance in ACE-III score. Any physical health conditions significantly associated with ACE-III score in the initial analysis would be clustered into one dichotomous variable. Similarly, any mental health conditions significantly associated with ACE-III score would be condensed into one dichotomous variable. These two variables would be entered into a multiple regression, along with any of the other five predictor variables from the initial analysis that were significantly associated with ACE-III score (anticholinergic medication, alcohol/substance misuse, sleep, premorbid functioning and pain) and two covariates, age and sex, for a possible total of up to 9 variables.

To explore research questions 3i) and 3ii), an additional hierarchical multiple regression analysis was planned tallying the total number of Chronic Health

Conditions for each participant and coding as a continuous score. The same process would be completed for Mental Health Conditions, to explore whether there is an additive effect of conditions on total ACE-III score. Influence of age and sex would be controlled for in this analysis.

Sample Size

Tabachnick & Fidell (2013) provide a formula for calculating sample size requirements for Multiple Regression: $N > 50 + 8m$ (where m = number of independent variables). According to this formula, a sample size of N=122 would be needed for a maximum of 9 variables to be included in the multiple regression analysis.

G* Power (Faul et al., 2007) was used to calculate sample size; for a medium effect size (f2=0.15), alpha-.05, power is 0.9, number of predictors = 9, a sample of n = 141 is suggested. Through discussions with colleagues within Older Person's Community Mental Health Teams, and given that the present study used retrospective data, it was anticipated that it would be feasible to obtain this sample size.

Ethics, Governance and Data Protection

Ethical approval was granted by East Midlands NHS Research Ethics Committee on 8th November 2022 (REC reference: 22/EM/0251; Appendix 2.8). As the study utilised existing data, Caldicott Guardian approval and Research & Innovation approval within the trust was also sought and granted. All study data extracted from patient note software was stored securely on NHS systems in line with the Data Protection Act (2018).

Results

Sample Characteristics

A total of 826 participants were identified as having received a neuropsychological assessment between 2013 and 2022 and were screened according to eligibility criteria for the study. Of these cases, 135 met inclusion criteria. Participants were predominantly of average premorbid intelligence (67.5%) and aged between 53-89 years old. The majority of cases (73.3%) scored below the upper recommended cut-off of 88 points for the ACE-III and just under half (48.9%) scored below the lower cut-off of 82. Clinical and demographic data for participants is summarised in **Table 6**.

Table 6 – Clinical and demographic characteristics of sample

Sample size *N*	**ACE-III Score** Mean (SD)	**Age** Mean (SD)	**Sex** *n* (%)	**Premorbid IQ** (% of sample)*	**Scoring below cut-offs of (a) 82 and (b) 88 on ACE-III** *n* (%)
135	80.86 (9.78)	71.3 (6.44)	F: 70 (52) M: 65 (48)	Borderline 0.8 Low average 5.8 Average 67.5 High Average 16.3 Superior 6.7	(a) 66 (48.9)** (b) 99 (73.3)***

Premorbid IQ presented as intellectual functioning range, as reported at neuropsychological assessment. Data available for 121 out of 135 cases.
****scoring below cut-off of 82***
*****scoring below cut-off of 88***

Prevalence of Conditions

Out of the total sample, 72% (*n* = 95) had at least one of the chronic health conditions predetermined as a variable of interest and 40.9% (*n* = 54) had a mental health condition (depression, anxiety or a chronic mental health issue). The average number of chronic health conditions for the sample was 1.32. For prevalence of variables in sample, compared to population estimates, please see **Table 7**.

Table 7 – Prevalence of health conditions in sample compared to population, and ACE-III scores for patients with and without the conditions.

Condition	Population Prevalence – Older Adults	Frequency in study sample n (%)		ACE-III Total Score Mean (SD)	
		With condition	Without condition	With condition	Without condition
Diabetes	15.8% in those aged 65+ (Scotland)	22 (16.7%)	110 (83.3%)	84.82 (7.08)	80.95 (8.73)
CKD	18.2% in those aged 60+ (UK)	24 (18.2%)	108 (81.8%)	80.83 (9.74)	81.76 (8.34)
CHD	23% in those aged 75+ (Scotland)	27 (20.5%)	105 (79.5%)	84.33 (7.1)	80.89 (8.81)
Autoimmune	Not available	5 (3.8%)	127 (96.2%)	76.60 (9.84)	81.79 (8.51)
COPD	9% for 65-74 year olds 12% for 75-84 year olds (Glasgow)	20 (15.2%)	112 (84.8%)	79.80 (9.5)	81.91 (8.41)
Osteoarthritis	Not available	45 (34.1%)	87 (65.9%)	80.27 (9.20)	82.28 (8.21)
Covid	Not applicable	3 (2.3%)	129 (97.7%)	82.33 (12.7)	81.57 (8.59)
Cancer	11.7% prevalence aged 65+ (Scotland)	19 (14.4%)	113 (85.6%)	82.37 (7.72)	81.46 (8.74)
Hypothyroidism	Not available	11 (8.3%)	121 (91.7%)	82.91 (8.38)	81.47 (8.62)
Pain	62% in 75+ (UK)	67 (50.8%)	65 (49.2%)	82.06 (9.07)	81.11 (8.08)
Depression	8% prevalence in 65-74 year olds 12% prevalence in adults (Scotland)	43 (32.6%)	89 (67.4%)	80.67 (7.71)	82.03 (8.97)
Anxiety	8% prevalence 2 or more symptoms of anxiety in those 75+ years (Scotland)	34 (25.8%)	98 (74.2%)	80.09 (7.67)	82.11 (8.85)
Chronic mental health condition	Not available	4 (3%)	128 (97%)	76.75 (15.5)	81.74 (8.33)
Anticholinergic medication	Not available	69 (52.3%)	62 (47%)	80.42 (8.74)	82.74 (8.27)
Alcohol/Substance misuse	Not available	19 (14.4%)	113 (85.6%)	80.89 (7.53)	81.71 (8.76)
Sleep difficulties	Not available	21 (15.9%)	111 (84.1%)	84.90 (7.44)	80.96 (8.66)

Preliminary Analyses

Preliminary analyses were performed to ensure data met assumptions required to carry out regression analysis. Inspection of the Normal Probability Plot indicated that residuals were broadly normal distributed. Analysis of multicollinearity for all predictor variables indicated high correlation (r = .71) between two variables, osteoarthritis and pain. Inspection of box-plots identified 3 outliers, constituting extremely low total scores on the ACE-III (46, 50 and 50). These cases (and all corresponding variable data for those participants) were removed, reducing total sample to n=132. Missing values analysis (MVA) was performed and identified 1 missing data point for anticholinergic medication and 14 missing data points for Premorbid IQ (10.9% of cases). MVA established that there was no evidence that data were systematically missing (Little's MCAR test not significant, p >0.05) and so cases were excluded listwise for all relevant analyses.

Linear Regression

As per the first stage of the analysis plan, univariate linear regressions were run for all of the 17 predictor variables against ACE-III score. From this analysis, only one variable, premorbid IQ, was a significant predictor of ACE-III score, accounting for 15% of variance [$F(1,116) = 20.53$, $p < .001$]. This influence remained even when controlling for age and sex, with premorbid IQ accounting for 12.7% of variance in ACE-III score ($F = 20.55$, $p < .001$). Premorbid IQ was weakly positively correlated with ACE-III total score (R = .39). No other predictor variables in the analysis made a statistically significant contribution towards variation in ACE-III score (for results for all variables see Appendix 2.7).

Given that premorbid IQ was the only predictor variable from the initial analysis that was significantly associated with ACE-III score, further planned analysis to explore research question 2) was not performed. However to explore research question 3) hierarchical multiple regression was carried out to assess whether cumulatively there was an influence on ACE-III score of number of i) chronic

physical health conditions ii) mental health conditions iii) anticholinergic medication. Number of exposures for each of these 3 variables was tallied for each participant and entered into a hierarchical multiple regression in the second block, with age and sex entered into the first block. This model was not significant [F (5, 125) = 1.67, p = .148] and none of the variables were a significant predictor of ACE-III score.

Diagnostic Status

Clinical health records for participants were re-examined to identify subgroups, in terms of those participants who went on to receive a diagnosis of dementia outside of the timeframe for inclusion criteria in this study (>12 months after neuropsychological assessment), those who received a diagnosis of Mild Cognitive Impairment (MCI) and those who have not received a diagnosis of either MCI or a dementia in the years proceeding assessment to present day. For mean ACE-III scores and boxplots for subgroups, please see **Table 8** below and **Figure 4**.

Table 8 – Mean ACE-III score and diagnostic status for sample

Diagnosis status	n	ACE-III score (Mean, SD)
Dementia diagnosis*	35	80.46 (7.16)
MCI	45	79.44 (8.27)
No diagnosis	52	84.21 (9.15)
Whole sample	132	81.59 (8.58)

Dementia diagnosis >12 months after neuropsychological assessment
MCI = Mild Cognitive Impairment

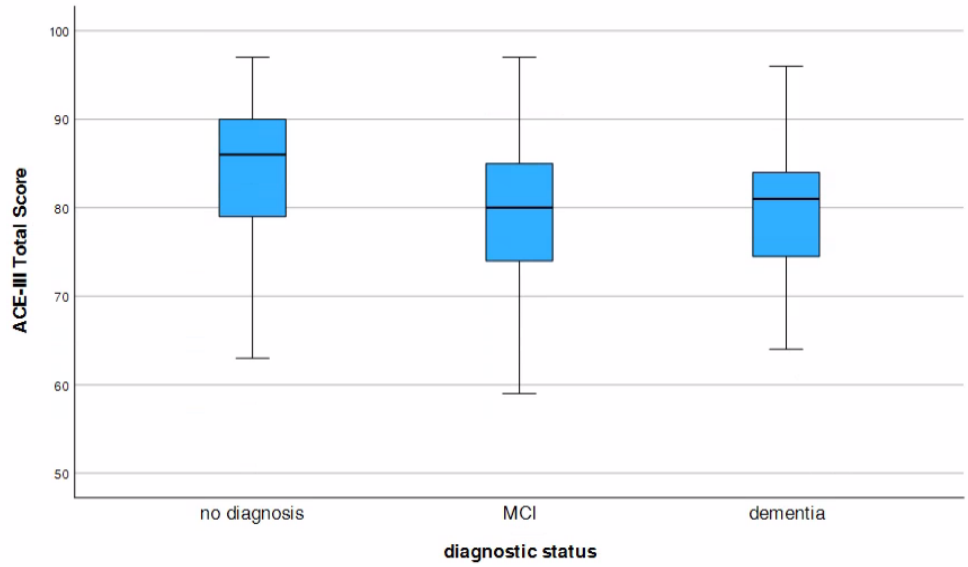

Figure 4 – Box plots for ACE-III score for subgroups by diagnostic status

A one-way ANOVA was performed to explore the impact of diagnostic status (MCI, dementia, no diagnosis) on ACE-III score. A significant difference was found between groups on mean ACE-III score [$F(2, 131) = 3.35$, $p = <0.05$]. Post-hoc comparisons using Tukey's HSD test indicated that the MCI group scored significantly lower than the no diagnosis group ($p = 0.048$). There were no significant differences in mean ACE score between the dementia group and the MCI group ($p = .953$), or between the dementia group and no diagnosis group ($p = .153$)

Univariate linear regressions exploring the impact of predictor variables on ACE-III score were repeated with the 'no diagnosis' subgroup. Once again, only premorbid IQ was a significant predictor of ACE-III score, [$F(1,41) = 8.75$, $p < 0.01$] accounting for 17.6% of variance, which reduced to 12.3% when controlling for influence of age and sex.

Discussion

This current study explored the influence of presence of chronic physical and mental health conditions common in an older adult population on a widely used cognitive screen for dementia, the ACE-III. This study did not detect a statistically significant influence of exposure to any of these conditions on partcipants' total score on the ACE-III. The only predictor variable that contributed significantly towards variance in ACE-III scores, was participants' premorbid intellectual functioning. This influence of premorbid IQ remained consistent across analyses of both the total sample and a subgroup consisting of those who did not receive either an MCI or dementia diagnosis in the years following neuropsychological assessment. Association between premorbid IQ and total ACE-III score also remained when controlling for the influence of age and sex. Although the current study did not detect an effect of physical or health conditions on cognitive functioning, this finding could be attributed to a number of factors related to the sample and data which are discussed below, and does not necessarily indicate an absence of influence of these conditions on cognitive functioning.

Firstly, the patients in the study sample were all memory clinic attendees and therefore all presented with a degree of subjective and/or objective cognitive impairment. Within this sample, there were no 'healthy controls' per se; the prevalence of health conditions within the sample was high (72% had at least one chronic health condition, 50.2% reporting pain symptoms or had a condition associated with pain) but nonetheless broadly reflective of the multi-morbidity of health conditions observed in the wider older adult population in the UK. This lack of a 'healthy' control group in a relatively small sample (*N* = 135) of individuals who by nature of having been referred for a neuropsychological assessment present with some complexity, may have made it difficult to differentiate the effects of any one health variable on cognitive functioning.

Although clinical notes for a large number of potential participants were screened, many did not meet inclusion criteria for the study, resulting in a smaller sample that was underpowered and less likely to be able to detect any

possible effect of health status on cognitive functioning. For three of the study variables (Covid-19, Autoimmune Disorders and Chronic Mental Health Conditions) the prevalence within the sample was too low (n = ≤5) to be able to meaningfully explore potential influence of these conditions. A surprising finding was the superior average performance on the ACE-III for individuals with some health conditions in the analysis (e.g. diabetes, coronary heart disease, hypothyroidism), compared to those without these conditions. This difference in performance was not able to be explained by demographic differences between groups and may be an anomaly that would not be replicated in a larger sample size of individuals with these conditions, or may be attributable to some other factor not explored in this study. Comparatively, many of the studies that have demonstrated a significant association between specific chronic health conditions and cognitive impairment, have employed much larger sample sizes (e.g. Thakur et al., 2010; Hampshire et al., 2021). Small effects have been demonstrated in previous research for impairment in executive functioning (*d* = -0.33), processing speed (*d* = -0.33) and verbal memory (*d* = -0.26) in individuals with diabetes (Palta et al., 2014), impairment in overall cognitive functioning in men (*d* = -.21) and women (*d* = -.15) with Coronary Heart Disease (Singh-Manoux et al., 2003) and significant associations between pain intensity and working memory performance in individuals with chronic pain (*r* = -0.38) (Oosterman et al., 2011). For those conditions linked to domain-specific impairments rather than impairment in general cognitive functioning, a brief cognitive screen such as the ACE-III may be less sensitive than a more comprehensive neuropsychological assessment battery.

Although prevalence of physical health conditions in the sample was broadly representative of population estimates, anxiety and depressive symptoms were overrepresented in this sample, compared to prevalence estimates for the country. This may be explained by the referral pathways into memory clinic assessments, which are sometimes generated by clinicians providing assessment and treatment of mental health difficulties for patients accessing older adult community mental health teams. In the course of that care provision, clinicians may query an underlying organic process in formulating

symptoms such as depressed mood that can also be observed in the early phases of a dementia. Indeed, as mentioned in the earlier chapter, differentiating affective symptoms as part of underlying mood disorder from early symptoms of a dementing process, can be challenging in clinical practice (Potter & Steffens, 2007).

Another challenge of the current study was use of existing data. Whilst medical records could be accessed to obtain variable information for chronic health condition diagnoses, variables such as pain, sleep difficulties and alcohol/substance misuse were reliant on consistent exploration and reporting of these conditions by clinicians in neuropsychological assessment reports as well as self-reporting of difficulties by patients at assessment. Information on the frequency, severity or duration of these conditions could not be ascertained from the data. More objective or consistent measurements of these variables may have been able to more accurately explore any potential influence of these on cognitive functioning.

A large number of health variables of interest were included in this study. Other options for data reduction could have been considered to reduce the number of variables. For example, it may have been possible to run a cluster analysis on the large number of health conditions included to examine whether particular conditions are more likely to co-occur as clusters. This may have allowed a cluster score (number of conditions within the cluster) to be derived for each of the clusters identified and this would have allowed a regression analysis to be run with fewer variables. However a limitation of this approach would be that clusters would be simply based on co-occurrence of conditions and not based on association with possibility of cognitive impairment. Another approach may have been to identify a subset of health conditions considered to have the strongest impact on cognition based on evidence from the literature and to sum the number of conditions present from this subset.

This study observed a wide distribution of scores on the ACE-III in a sample of individuals who were not diagnosed with a dementia in the year following cognitive assessment. The mean ACE-III score for the whole sample (80.86) fell below both the upper (88) and lower recommended cut-offs (82) on the

screen. At the lower cut-off of 82, the index paper for the ACE-III identified sensitivity and specificity rates of 0.93 and 1.0 respectively, indicating no false positives in their test sample (Hsieh et al., 2013), which is in contrast to the present study's initial analysis. However, further examination of the data in the present study identified that a proportion of individuals from the original sample (26%) received a dementia diagnosis in the years proceeding assessment and a further proportion of the sample (34%) were given a diagnosis of Mild Cognitive Impairment. Lower than expected scores for the sample could therefore represent the beginnings of a dementing process in some individuals which has been correctly detected by the ACE-III, or a mild cognitive impairment which may convert into a dementia in time. Indeed a strength of the ACE-III above other commonly used cognitive screens such as the MoCA and the MMSE is its sensitivity to early phases of dementia and MCI in comparison to other screens (Senda et al., 2020).

Interestingly, the mean ACE-III score for the MCI group (79.44) was the lowest in the sample– although similar to the dementia group (80.46) – and significantly lower than the no diagnosis group (84.21). Although this study found a comparable ACE-III performance in MCI and dementia groups, in the case of those with dementia, diagnoses were given in the years following assessment, not at the point of ACE-III administration and so captured a time-point of relatively less impaired cognitive functioning. Furthermore, MCI and dementia participants were likely differentiated at the point of diagnosis by functional status, explored qualitatively by clinicians through informant and self-reported accounts.

The 'no diagnosis' group, although presenting with relatively superior performance compared to the other groups, still on average scored below the higher cut-off of 88 on the ACE-III. This study could not detect an influence of physical or mental health variables included in this analysis that could account for these lower scores, however the sample size for this subgroup was small (n=52). Terpening et al. (2010) examined the utility of the predecessor to the ACE-III, the ACE-R (Mioshi et al., 2006) for dementia diagnosis in a similar sample that included those with psychiatric disorders and medical comorbidities. Amongst the eight false positives in their study, patients had

medical comorbidities, polypharmacy and depressive disorder and scores ranged from 72-81 on the ACE-R. However, their study also included a relatively small sample size (40 individuals in the no-dementia group) and the influence of these comorbidities was not explored statistically. Their false positives group also included three individuals with a history of stroke (which was excluded for the present study) and two with an MCI diagnosis. However both Terpening et al.'s (2010) study and the current study used samples that are representative of the complexity in presentations often observed in clinical practice.

This current study supported Stott et al.'s (2017) findings that ACE-III scores are significantly associated with premorbid intelligence, with lower premorbid intellectual functioning as measured by the Test of Premorbid Functioning (TOPF) associated with lower ACE-III scores. In the current study, when controlling for age and sex, Premorbid IQ accounted for 12.7% of variance in ACE-III scores in total sample and 12.3% in the subgroup with no dementia diagnosis. The current study however was less precise in exploration of this factor, as scores on the TOPF were not available from the source of data, so estimated ranges of Premorbid IQ from the TOPF were utilised as reported on neuropsychological assessment reports. Comparatively, Stott et al. (2017) looked at both demographic-adjusted and unadjusted estimates of premorbid IQ as generated by the TOPF. However, in their analyses, the authors found that adjusting for influence of premorbid IQ did not result in improvements in diagnostic accuracy of the ACE-III for detecting a dementia; the authors suggested that the upper recommended cut-off of 88 still maintains excellent accuracy for dementia screening and is robust to variance in pre-morbid IQ. Their control sample was, however, of above average intelligence which may limit generalisability of findings to those with lower premorbid IQ, who would arguably be at higher risk of false positives for dementia. In our sample, the vast majority of participants (67.5%) were of average intelligence, however individuals with below average intelligence were a small proportion of the sample (5.1%).

Conclusions

The current study was not able to detect an influence of presence of chronic physical health and mental health conditions on performance on the ACE-III cognitive screen in a memory clinic sample. This was despite the majority of the sample scoring below recommended cut-offs on the ACE-III but not receiving a dementia diagnosis at the time of assessment. Physical and mental health comorbidities were prevalent amongst participants and the potential interplay and influence of these conditions on cognitive functioning was difficult to examine in a relatively small sample utilising existing data. This study originally intended to explore the potential influence of different health variables on performance on the ACE-III, with an expectation that, in the sample of people who did not have a dementia diagnosis, there would be some people who did not have conditions considered likely to impact on cognition. However, amongst the participants in the eventual sample, there was a high proportion with one or more conditions considered likely to impact cognition, with 72% of participants having at least one chronic physical health condition and 41% having a mental health condition. This may have impacted on the possibility of detecting the effect of individual physical or mental health conditions on cognitive functioning. Additionally, further investigation of the sample highlighted that, although they did not receive a diagnosis of dementia within 12 months, a substantial proportion of participants went on to receive a diagnosis in the years following their assessment, suggesting that cognitive impairment was potentially already present.

Further research could seek to explore the potential influence of these conditions in a larger sample, to better understand what health factors may be contributing towards false positive classifications amongst non-demented individuals. This study highlights the complexity of presentations observed in a memory clinic setting and the importance of utilising the ACE-III in addition to a clinical history as part of a dementia screening process. Given the influence of premorbid intellectual functioning on ACE-III scores, the development of norms that are adjusted for pre-morbid intellectual ability may be of benefit in improving screening accuracy of this tool.

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Appendices

Appendix 1.1 – PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 11
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 11
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 12
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 14
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 15
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1.2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 16
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 16
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 16
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 16-18
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 18
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 18
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	n/a
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 18
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 18
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 18
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	n/a
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 18
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 27

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 19
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 19
Study characteristics	17	Cite each included study and present its characteristics.	Page 22-23
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 26
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 29
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 22-23 Page 26
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 27-29
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 29
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	n/a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 30
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 29
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 30-32
	23b	Discuss any limitations of the evidence included in the review.	Page 32-33
	23c	Discuss any limitations of the review processes used.	Page 32-33
	23d	Discuss implications of the results for practice, policy, and future research.	Page 34
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 14
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 14
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 14
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	n/a
Competing interests	26	Declare any competing interests of review authors.	Page 34
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 22-25

Appendix 1.2 – Search Syntax for Databases

Database	Search Syntax
MEDLINE (OVID)	1. ACE-III.mp. 2. Addenbrooke*.mp 3. ACE-R.mp 4. 1 or 2 or 3 5. depress*.mp. 6. affective disorder.mp 7. mood disorder.mp 8. depression/ 9. exp depressive disorder/ 10. 5 or 6 or 7 or 8 or 9 11. 4 and 10
EMBASE (OVID)	1. ACE-III.mp. 2. Addenbrooke*.mp 3. ACE-R.mp 4. 1 or 2 or 3 5. depress*.mp. 6. depression/ 7. affective disorder.mp 8. mood disorder.mp 9. 5 or 6 or 7 or 8 10. 4 and 9
PsycINFO (EBSCOhost)	1. TX ACE-III 2. TX Addenbrooke* 3. TX ACE-R 4. S1 OR S2 OR S3 5. TX depress* 6. “DE “Major Depression” OR “DE “Anaclitic Depression” or DE “Dysthymic Disorder” OR DE “Endogenous Depression” or DE “Late Life Depression” OR DE “Postpartum Depression” OR DE “Reactive Depression” OR DE “Recurrent Depression” OR DE “Treatment Resistant Depression” 7. DE “Depression (Emotion)” 8. TX Affective Disorder 9. TX Mood Disorder 10. S5 or S6 or S7 or S8 or S9 11. S4 AND S10
CINAHL (EBSCOhost)	1. TX ACE-III 2. TX Addenbrooke* 3. TX ACE-R 4. TX depress* 5. (MH “Depression+”) 6. TX affective disorder 7. TX mood disorder 8. S1 OR S2 OR S3 9. S4 OR S5 OR S6 OR S7 10. S8 and S9

Appendix 1.3 – JBI Checklist

JBI CRITICAL APPRAISAL CHECKLIST FOR ANALYTICAL CROSS SECTIONAL STUDIES

Reviewer_____Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 1.4 – Guidance on adaptations to JBI Checklist

Adaptions to JBI Checklist for Analytical Cross-Sectional Studies

Ratings – yes, no, unclear, n/a

	JBI Item	Additional information
1	Were the criteria for inclusion in the sample clearly defined?	Inclusion and exclusion criteria for the exposure and control groups clearly defined. Dementia clearly excluded from both groups.
2	Were the study subjects and the setting described in detail?	Describing the source of subjects, demographics, study location and time period. If study utilises participants from other studies, ensuring that a reference is provided and sample adequately described in that paper.
3	Was the exposure measured in a valid and reliable way?	Exposure group preferably defined by diagnosis of depression using recognised classification system (i.e. DSM, ICD). If the latter criteria not met, then a score above cut-off on a validated mood measure is acceptable though will be considered a less robust measure.
4	Were objective, standard criteria used for the measurement of the condition?	n/a for this review. Measurement of exposure already covered in criteria 3 of checklist
5	Were confounding factors identified?	Reporting age and education level for groups, and any health conditions which could significantly impact on cognition, if not excluded from sample already.
6	Were strategies to deal with confounding factors stated?	Either statistical analysis for effect of age and education on exposure, matching participants on these variables or controlling for these in analysis.
7	Were the outcomes measured in a valid and reliable way?	ACE administered by appropriately trained clinicians. Clearly stating what edition and language version of the ACE was utilised. Version has been validated for use in target sample and (unless aim of paper is to validate version of ACE, in which this item will not be applicable) and ideally study makes reference to cut-offs that have been established for version of ACE utilised.
8	Was appropriate statistical analysis used?	Reporting means and SDs OR median and IQ ranges for exposure and control group. Rationale for statistical analysis given and results clearly presented. Appropriate use of parametric or non-parametric tests according to distribution of the data.

Appendix 2.1 - Development of Study Variables

Physical Health

A review of epidemiological research was conducted to identify the most prevalent physical health conditions and mental health conditions in older adults in the study region. Where possible, prevalence of chronic diseases was sought for the study region (Glasgow) or more broadly for Scotland or the UK. There is no universal definition of what constitutes a chronic or 'long-term condition', but definitions variously make reference to conditions that are long-lasting, non-infectious and associated with impairment in functioning, with symptoms tending to be managed long-term rather than the underlying pathology associated with the disease being able to 'cured' or reversed. A list of 9 chronic health conditions (or categories of condition) were identified from reviewing the health literature and government data and health surveys for the study region:

1) Diabetes
2) Chronic Kidney Disease
3) Chronic Heart Disease
4) Autoimmune Disorders
5) COPD
6) Osteoarthritis
7) Covid-19
8) Cancer
9) Hypothyroidism

Dichotomous variables were created for all 9 health conditions (condition present or absent for each participant) and patient health records reviewed to determine condition status for each participant at the time of the cognitive assessment. Due to the novelty of the emergence of Covid-19 at the time of study development, this was coded as 'present' if participants had a diagnosis of Covid-19 ever recorded prior to cognitive assessment.

Pain

A list of painful conditions developed by the International Association for the Study of Pain (Classification of Chronic Pain, Second Edition – Revised, 2011) was used to inform this study (See Appendix 2.4). The list constitutes a range of conditions and syndromes associated with pain experiences, some of which are highly variable in their disease course, transient in nature, or in which the underlying pathology is able to be treated with medication or surgery and therefore not typically causing pain across the lifespan. The list was therefore split into those conditions that are likely to be causing frequent pain from the point of onset (Category A) and those that are highly variable, treatable or self-limiting (Category B). Pain was coded as present if a Category A condition was recorded on medical notes at any point prior to cognitive assessment and only coded as present for Category B conditions if a diagnosis of the condition was recorded within the 6 months preceding cognitive assessment (see Table below for summary).

Category A Conditions	
Criteria	Typically: - Lifelong from the point of onset and will not spontaneously resolve - Underlying pathology causing pain is typically not curable or reversible - Likely to be causing frequent pain following onset of condition
Coding	Pain coded as 'present' if diagnosis **ever recorded** on medical notes prior to cognitive assessment
Conditions	Peripheral neuropathy, central pain syndrome, fibromyalgia, rheumatoid arthritis, osteoarthritis, systemic sclerosis, angina pectoris, Crohn's disease, ulcerative colitis, chronic pancreatitis, peroneal muscular atrophy (charcot-marie-tooth disease), osteoarthritis, spinal stenosis
Category B Conditions	
Criteria	All other conditions from International Association for the Study of Pain (IASP) list.
Coding	Pain coded as 'present' if diagnosis of condition recorded **within the 6 months preceding cognitive assessment**

Self-reported symptoms of pain at the time of cognitive assessment, were also used to inform presence of pain. This information is typically recorded on the neuropsychological assessment report.

Mental Health

Research on the prevalence of psychiatric disorders in an older adult population is limited and there is substantial variation in estimated rates (Skoog et al., 2011), with studies primarily limited to exploring the prevalence of depressive disorders. Data available from public health surveys in the country of origin provided information on self-reported prevalence of symptoms of anxiety and depression (see Appendix 2.3) rather than psychiatric disorders assessed according to DSM-V criteria (American Psychiatric Association, 2013). An epidemiological study of psychiatric conditions in 3142 European older adults found the most prevalent to be anxiety disorders (17.2%), affective disorders (13.7%) and substance misuse disorders (8.9%), with an overall prevalence of any mental health condition of 35.2% across a 12 month period (Andreas et al., 2017). Taking into consideration the presentations frequently observed in an older adult memory clinic population, as well as their potential impact on cognition, three categories of mental health conditions were developed for inclusion in this study:

1. Depressive disorders – including major depressive disorder, recurrent depression and dysthymia
2. Anxiety disorders – including GAD, Agoraphobia, Panic Disorder, OCD, Social Phobia and specific Phobias
3. Chronic Mental Health Conditions – including schizophrenia, bipolar disorder and psychosis

Psychiatric disorders are assigned equivalent 'problem' labels on patient note software within NHS Greater Glasgow and Clyde. Three dichotomous variables will be created for the presence or absence of a depressive disorder, anxiety disorder or chronic mental health condition respectively. Depressive disorders will be recorded as present if a psychiatrist has ever recorded any of the disorders within this category as a problem label on patient notes, or if a score above cut-off on a validated measure of depressed mood is recorded within 6 months of ACE-III administration. Similarly, an

anxiety disorder will be recorded as present if a psychiatrist has ever recorded any of the disorders within this category as a problem label on patient notes, or if a score above cut-off a validated measure of anxiety has been recorded within 6 months of ACE-III administration. Chronic Mental Health conditions will be recorded as present if a psychiatrist has ever recorded any of the disorders within this category as a problem label on patient notes.

Anticholinergic Medication

A list of commonly prescribed Anticholinergic medications detailed in a study by López-Álvarez et al., (2019) will be used (see Appendix 2.6) to code for this variable. Medication history is recorded on electronic patient note records, along with a timestamp detailing exactly when that medication was prescribed and when a prescription ended. Anticholinergic medication will be a dichotomous variable, coded as present if the patient is recorded as having an active prescription for any medication from this list, at the time of completing the ACE-III.

Premorbid Functioning

An assessment of premorbid functioning is typically completed during neuropsychological assessment through administration of the Test of Premorbid Functioning (TOPF). Performance on the TOPF will be captured by extracting estimated range of premorbid intellectual functioning (extremely low, borderline, low average, average, high average, superior, very superior) from neuropsychological assessment reports and recording as a categorical variable.

Alcohol/Substance Misuse

Presence of alcohol/substance misuse difficulties will be coded if an equivalent 'problem' label has ever been recorded by a psychiatrist on patient notes, or the patient self-reports a history of alcohol or substance misuse or dependency.

Sleep difficulties

Sleep difficulties will be coded as present if a sleep disorder problem level has even been recorded on patient notes by a psychiatrist, or if sleep problems are noted as being present in the neuropsychological assessment report.

Demographic Variables

Patient age and gender will be recorded and the influence of these will be controlled for in the analysis.

ACE-III

Performance on ACE-III will be captured by extracting patients' total ACE-III score from electronic notes. This will be inputted into analysis as a continuous variable.

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Appendix 2.2 – Prevalence of Chronic Health Conditions in Older Adults

Chronic Health Conditions – Prevalence in UK/Scottish population		
Condition	Estimated Prevalence – Scottish Adults	Estimated Prevalence – Older Adults
Diabetes Mellitus *Includes Type 1 & Type 2*	5.6% (Source – Scottish Diabetes Survey 2018)	15.8% in those aged 65+ (Source – Scottish Diabetes Survey 2018)
Chronic Kidney Disease	3.08% (Source – Quality Outcomes Framework, 2018-2019) 2.75% prevalence in NHS GG&C (Source – Quality Outcomes Framework, 2018-2019)	18.2% for UK adults aged 60+ years old (Source – Hirst et al., 2020)
Chronic Heart Disease *Includes cardiac arrest, myocardial infarction & angina* (also known as coronary artery disease and	5% (Source - Scottish Health Survey 2018-2019)	23% prevalence in adults aged 75+ years (Scottish Health Survey 2018-2019)

Ischaemic heart disease)		
Autoimmune	Not available for Scottish Adults Estimated 6% prevalence in the UK population (all ages) (Source - Connect Immune Research, JDRF, 2018)	Not available
COPD *includes emphysema and chronic bronchitis*	4% prevalence in Scottish adults (Source - Scottish Health Survey 2018)	In GG&C: 6.26% prevalence for adults aged over 45+ years 9.94% for 65-74 12.77% for 75-84 (Source – Levin et al., 2020)
Osteoarthritis	7% prevalence in Scottish adults (Source – Scottish Burden of Disease Study 2016)	Not available
Covid-19	735,750 people tested positive in Scotland (all time – as of 3/12/21) (Source – Scottish Government, 2021)	Not available
Cancer	3.52% prevalence in Scottish adults (Source – Scottish Cancer Registry, 2017)	11.71% prevalence in Scottish adults aged 65+ (Source – Scottish Cancer Registry, 2017)

Other Health Conditions		
Stroke/TIA (or Cerebrovascular Disease)	3% of all adults in 2019 (Source - Scottish Health Survey 2019)	11% in those aged over 75 (Source – Scottish Health Survey 2019)
Thyroid Disorders *Includes hyperthyroidism and hypothyroidism*	Estimated UK wide prevalence is 3.6% in all ages (Source - Ingoe et al., 2017)	35% of individuals with hypothyroidism are over the age of 70 in the UK. (Source - Ingoe et al., 2017)
Chronic Pain	Estimated prevalence of 14.1% Scottish Adults in the Grampian region (Source – Smith et al., 2001)	Estimated 62% prevalence in UK older adults aged 75+ (Source – Fayaz et al., 2016)

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Appendix 2.3 – Prevalence of Mental Health Conditions in Older Adults

Presentation	Estimated Prevalence – Scottish Adults	Prevalence in Older Adults
Depression	12% prevalence Scottish Adults (Source - Scottish Health Survey 2019)	8% prevalence in 65-74 year olds (Source – Scottish Health Survey 2019)
Anxiety	14% of Scottish adults reported 2 or more symptoms of anxiety (Source – Scottish Health Survey 2019)	8% of those aged 75+ reported 2 or more symptoms of anxiety (Source – Scottish Health Survey 2019)

References

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Appendix 2.4 – List of Painful Conditions

Taken from the International Association for the Study of Pain (Classification of Chronic Pain, Second Edition – Revised, 2011)

Part 1 - A - Relatively Generalized Syndromes

Peripheral neuropathy
Stump pain
Phantom pain
Complex Regional Pain Syndrome
Central pain
Syringomyelia
Polymalgia Rheumatica
Fibromyalgia
Fibrositis
Rheumatoid Arthritis
Osteoarthritis
Calcium Pyrophosphate Dihydrate Deposition Disease (CPPD)
Gout
Hemophilic Arthropathy
Pain of Psychological Origin - Muscle Tension
Pain of Psychological Origin - Delusional or Hallucinatory
Pain of Psychological Origin - Hysterical, Conversion, or Hypochondriacal
Pain of Psychological Origin - Associated with Depression
Factitious Illness and Malingering
Regional Sprains or Strains
Sickle Cell Arthropathy
Purpuric Arthropathy
Stiff Man Syndrome
Paralysis Agitans
Epilepsy
Polyarteritis Nodosa
Psoriatic Arthropathy and Other Secondary Arthropathies
Painful Scar
Systemic Lupus Erythematosis, Systemic Sclerosis and Fibrosclerosis, Polymyositis and Dermatomyositis
Infective Arthropathies
Traumatic Arthropathy
Osteomyelitis
Osteitis Deformans
Osteochondritis
Osteoporosis
Muscle Spasm
Local Pain, No Cause Specified
Guillain-Barré Syndrome

Part 1 - F - VISCERAL AND OTHER SYNDROMES OF THE TRUNK APART FROM

SPINAL AND RADICULAR PAIN

XVII. Visceral and Other Chest Pain

Acute Herpes Zoster
Postherpetic Neuralgia
Other Postinfectious and Segmental Peripheral Neuralgia
Angina Pectoris
Myocardial Infarction
Pericarditis
Aneurysm of the Aorta
Disease of the Diaphragm
Carcinoma of the Esophagus
Slipping Rib Syndrome
. Postmastectomy Pain Syndrome: Chronic Nonmalignant
Late Postmastectomy Pain or Regional Carcinoma
Post-thoracotomy Pain Syndrome
Internal Mammary Artery Syndrome
Tietze's Syndrome-Costo-Chondritis
. Fractured Ribs or Sternum
Xiphoidalgia Syndrome
Carcinoma of the Lung or Pleura

XVIII. Chest Pain of Psychological Origin

Muscle Tension Pain
Delusional Pain
Conversion Pain
With Depression

XIX. Chest Pain Referred from Abdomen or Gastrointestinal Tract

Subphrenic Abscess
Herniated Abdominal Organs
Esophageal Motility Disorders
Esophagitis
Reflux Esophagitis with Peptic Ulceration
Gastric Ulcer with Chest Pain
Duodenal Ulcer with Chest Pain
Thoracic Visceral Disease with Pain Referred to Abdomen

XX. Abdominal Wall Pain

Acute Herpes Zoster
Postherpetic Neuralgia
Segmental or Intercostal Neuralgia
Twelfth Rib Syndrome
Abdominal Cutaneous Nerve Entrapment Syndrome

XXI. Abdominal Pain of Visceral Origin

Cardiac Failure
Gallbladder Disease
Post-cholecystectomy Syndrome
Chronic Gastric Ulcer
Chronic Duodenal Ulcer
Carcinoma of the Stomach

Carcinoma of the Pancreas
Chronic Mesenteric Ischemia
Crohn's Disease
Ulcerative Colitis
Chronic Constipation
Diverticular Disease of the Colon
Carcinoma of the Colon
Gastritis and Duodenitis
Dyspepsia and Other Dysfunctional Disorders in Stomach with Pain
Radiation Enterocolitis
Post-Gastric Surgery Syndrome, Dumping
Chronic Pancreatitis
Carcinoma of the Liver or Biliary System
Carcinoma of the Kidney (Grawitz Carcinoma)
Recurrent Abdominal Pain in Children
XXII. Abdominal Pain Syndromes of Generalized Diseases

Familial Mediterranean Fever (FMF)
Abdominal Migraine
Intermittent Acute Porphyria
Hereditary Corproporphyria
Variegate Porphyria

XXIII. Chronic Pelvic Pain Syndromes

Perineal Pain Syndrome
Bladder Pain Syndrome
Prostate Pain Syndrome
Scrotal Pain Syndrome
Testicular Pain Syndrome
Epididymal Pain Syndrome
Penile Pain Syndrome
Urethral Pain Syndrome
Postvasectomy Scrotal Pain Syndrome
Vulvar Pain Syndrome
.Generalized Vulvar Pain Syndrome
.Localized Vulvar Pain Syndrome
Endometriosis-Associated Pain Syndrome
Chronic Pelvic Pain Syndrome with Cyclical Exacerbations
Primary Dysmenorrhea
Pelvic Floor Muscle Pain Syndrome
Coccyx Pain Syndrome
Irritable Bowel Syndrome
Chronic Anal Pain Syndrome
Intermittent Chronic Anal Pain Syndrome
Abdominal Pain: Visceral Pain Referred to the Abdomen (See XVII-6, Pericarditis; XIX-2, Herniated.
Abdominal Organs; XVII-7, Aneurysm of the Aorta; and XVII-8, Diseases of the Diaphragm)

XXIV. Diseases of the Bladder, Uterus, Ovaries, Testis, and Prostate, and their Adnexa

Mittelschmerz

Secondary Dysmenorrhea With Endometriosis
Secondary Dysmenorrhea With Adenomyosis or Fibrosis
Secondary Dysmenorrhea With Congenital Obstruction
Secondary Dysmenorrhea With Acquired Obstruction
Endometriosis
Adenomyosis
Chronic Pelvic Inflammatory Disease (PLD)
Ovarian Pain
Pain from Urinary Tract
Pain Associated with Testicular Disease
Carcinoma of the Bladder
Carcinoma of the Prostate
Cervical Cancer
Uterine Cancer
Ovarian Cancer

XXV. Pain in the Rectum, Perineum, and External Genitalia

Neuralgia of Iliohypogastric, Ilio-Inguinal, or Genito-Femoral Nerves Testicular Pain
Rectal, Perineal, and Genital Pain of Psychological Origin
Pain of Hemorrhoids
Proctalgia Fugax
Ulcer of Anus or Rectum
Injury of External Genitalia
Carcinoma of the Prostate

Part 1 - H LOCAL SYNDROMES OF THE LOWER LIMBS

XXXI. Local Syndromes in the Leg or Foot: Pain of Neurological Origin

Lateral Femoral Cutaneous Neuropathy (Meralgia Paresthetica)
Obturator Neuralgia
Femoral Neuralgia
Sciatic Neuralgia
Interdigital Neuralgia of the Foot (Morton's Metatarsalgia)
Injection Neuropathy
Gluteal Syndromes
Piriformis Syndrome
Painful Legs and Moving Toes
Metastatic Disease
Peroneal Muscular Atrophy (Charcot-Marie-Tooth Disease)

XXXII. Pain Syndromes of Hip and Thigh of Musculoskeletal Origin

Ischial Bursitis
Trochanteric Bursitis
Osteoarthritis of the Hip
XXXIII. Musculoskeletal Syndromes of the Lower Limbs

Spinal Stenosis
Osteoarthritis of the Knee
Night Cramps
Plantar Fasciitis

Appendix 2.5 – Coding of Variables to be Included in Initial Analysis

Chronic Health Conditions			
Condition Category	Includes	Coding	Variable Type
Type 2 Diabetes	*Includes Type 2 Diabetes only*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Chronic Kidney Disease	*Includes Chronic Kidney Disease*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Chronic Heart Disease	*Includes cardiac arrest, myocardial infarction & angina* (also known as coronary artery disease and ischaemic heart disease)	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Autoimmune Disorder	*Includes MS, Type 1 Diabetes, Rheumatoid arthritis, Coeliac's Disease, Crohn's disease, Addison's disease and Lupus* (excluding Hypothyroidism)	Diagnosis recorded on medical notes at any point prior to cognitive assessment. .	Dichotomous (present/absent)
COPD	*includes emphysema and chronic bronchitis*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Osteoarthritis	*Includes Osteoarthritis only*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Covid-19	*Includes any variant of Covid-19*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Cancer	*Includes any form of cancer*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)
Hypothyroidism	*Includes hypothyroidism only*	Diagnosis recorded on medical notes at any point prior to cognitive assessment.	Dichotomous (present/absent)

Chronic Pain	See Appendix 4 for list of painful conditions	EITHER: Category A conditions – Diagnosis of condition recorded on medical notes at any point prior to cognitive assessment. *OR* Category B conditions – recorded on medical notes within the 6 months preceding cognitive assessment *OR* self-reported symptoms of pain noted on neuropsychological assessment report.	Dichotomous (present/absent)
Mental Health			
Category	Includes	Coding	Variable Type
Depressive Disorder	Major depressive disorder, recurrent depression, dysthymia	EITHER: Equivalent 'problem' label of a mood disorder ever recorded by a psychiatrist on patient notes software OR Score above cut-off on PHQ-9, completed within 6 months of ACE-III	Dichotomous (present/absent)
Anxiety Disorder	Generalised Anxiety Disorder (GAD), Panic Disorder, Agoraphobia, OCD, Social Phobia, Specific Phobias	EITHER: Equivalent 'problem' label of an anxiety disorder ever recorded by a psychiatrist on patient notes OR Score above cut-off on GAD-7 completed, within 6 months of ACE-III	Dichotomous (present/absent)
Chronic Mental Health Condition	Schizophrenia, Psychosis or Bipolar disorder	Equivalent 'problem' label of ever recorded by a psychiatrist on patient notes	Dichotomous (present/absent)
Other Variables			
Category	Includes	Coding	Variable Type
Anticholinergic Medication	See Appendix 2.6 for list of medications	On any medication from list in Appendix 2.6 at the time of ACE-III	Dichotomous (present/absent)

Alcohol/Substance Misuse	Alcohol or any illicit substances	EITHER: Equivalent 'problem' label ever recorded by a psychiatrist on patient notes OR: Self-reported history of alcohol or substance misuse or dependency by patient	Dichotomous (present/absent)
Sleep Difficulties	Any DSM-V sleep disorder	EITHER: Equivalent 'problem' label to a DSM-V sleep disorder ever recorded by a psychiatrist on patient notes OR Sleep difficulties noted on neuropsychological assessment report.	Dichotomous (present/absent)
Premorbid Functioning	Premorbid IQ estimated range	Premorbid IQ Ranges: extremely low borderline low average average high average superior very superior	Categorical
Age			Continuous
Gender			Categorical

Appendix 2.6 – List of common anti-cholinergic medications

From López-Álvarez et al., (2019)

Neuropsychiatric Drugs with Anticholinergic Side Effects	
Tricyclic Antidepressants Amitriptyline Clomipramine Desipramine Imipramine **Antipsychotics** Chlorpromazine Clozapine Fluphenazine Loxapine Olanzapine Perphenazine **Antiepileptics** Carbamazepine Oxcarbazepine **Anticholinergics as such** Benztropine Biperiden Trihexyphenidyl	High Anticholinergic Load
Antidepressants Fluoxetine Fluvoxamine Mirtazapine Nortriptyline Paroxetine Sertraline Trazadone **Antipsychotics** Haloperidol Quetiapine Ziprasidone **Benzodiazepines** Alprazolam Chlordiazepoxide	Low-Moderate Anticholinergic Load

Clonazepam Clorazepate Diazepam Flurazepam Lorazepam Midazolam **Antiepileptics** Valproate **Antiparkinsonians** Amantadine Bromocriptine Carbidopa-Levodopa Pramipexol Selegiline **Opioids** Codeine Fentanyl Morphine Tramadol	
Common non-psychoactive drugs with anticholinergic effects	
Antihistamines Diphenhydramine Hydroxyzine Loratadine **Antispasmodics** Loperamide **Antiulcer** Cimetidine Ranitidine **Bronchodilators** Fluticasone-salmeterol **Cardiovascular** Digoxin Dilitiazem Warfarin **Corticoids** Cortisone Dexamethasone Methylprednisolone Prednisone	

Diuretics
Captopril
Chlortalidone
Furosemide

Urological
Oxybutynin
Tolterodine

Appendix 2.7 – Table of Results for Univariate Linear Regressions with ACE-III Score

Variable	β	R^2	Adjusted R^2	Sig.
Premorbid IQ	.39	.15	.14	<.001*
Diabetes	.17	.03	.02	.053
CKD	-.04	.00	-.01	.634
CHD	.16	.03	.02	.062
Autoimmune	-.17	.01	.01	.186
COPD	-.09	.01	.00	.312
Osteoarthritis	-.11	.01	.01	.203
Covid-19	.01	.00	-.01	.880
Cancer	.04	.00	-.01	.671
Hypothyroidism	.05	.00	-.01	.596
Pain	.06	.00	-.01	.526
Sleep	.17	.03	.02	.053
Anticholinergic Medication	-.14	.02	.01	.122
Alcohol/Substance Misuse	-.03	.00	-.01	.704
Depression	-.08	.01	-.01	.395
Anxiety	-.10	.01	.00	.237
Chronic Mental Health	-.10	.01	.00	.253

Appendix 2.8 – REC Approval

NHS
Health Research Authority

East Midlands - Nottingham 1 Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0207 104 8115

14 November 2022

Professor Jonathan Evans
Administration Building
Gartnavel Royal Hospital
1055 Great Western Road
G120XH

Dear Professor Evans

Study title: **Exploring the influence of physical and mental health factors on older adults' performance on the Addenbrookes Cognitive Examination, 3rd Edition (ACE-III)**
REC reference: **22/EM/0251**
IRAS project ID: **317059**

The Research Ethics Committee (REC) reviewed the above application at the meeting held on 08 November 2022. Thank you for attending to discuss the application.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC suggested the following changes could be made in order to improve documentation. Please note these changes are **recommendations only** and are not a requirement of the Favourable Opinion.

Appendix 2.9 – MRP Protocol

https://osf.io/v6e3k/?view_only=3ebf3acd1d6948678b2d41c84233735c