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Measuring Dementia Symptoms: Using the Mini-Mental State Examination as a Surrogate for the Clinical Dementia Rating Scale when Evaluating Dementia Interventions

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ABSTRACT

Background: Recently, a number of non-pharmacological interventions for dementia symptoms were evaluated using Cost-Benefit Analysis and found to be both effective and socially worthwhile. In these studies, dementia symptoms were measured by the Clinical Dementia Rating (CDR) scale. Although the CDR is the most comprehensive and reliable instrument for measuring dementia symptoms, common practice is to use the Mini-Mental State Examination (MMSE) as a substitute. The objective of this paper is to examine the relationship between the two measures, using a large national data set, in order that one can meaningfully convert evaluations using the MMSE into the more comprehensive CDR version.

Methods: The main analysis involves using regression models to estimate the relationship between the two dementia symptom methods in a large, national, panel data set. Four regression specifications are presented according to which controls are selected. The subsequent analysis entails looking at a case study of a particular dementia intervention, that of vision correction, to see whether in practice the MMSE and CDR give similar CBA decisions results when data on both measures were actually available.

Results: We find that multiplying a MMSE outcome measure by 0.4 will provide a valid approximation for the CDR when the latter measure is not available. This approximation was reasonably robust to a whole range of controls that were included. The case study of vision correction provided further corroborative evidence that the MMSE can be a practical surrogate for the CDR.

Conclusions: The CDR can be approximated by the MMSE when carrying out a CBA of any dementia symptoms intervention. Benefits estimated using the CDR can readily be transferable to become the benefits using the MMSE.

Keywords: Dementia; symptoms; CDR, MMSE, interventions; costs; benefits.

1. Introduction

Dementia is a cognitive disorder that leads to symptoms that interfere with a person's ability to carry out activities of daily living. An estimated 6.7 million Americans age 65 and older are living with Alzheimer's in 2023, which is the main type of dementia.[1] By 2050, the number of people age 65 and older with Alzheimer's may grow to a projected 12.7 million, if there are no medical breakthroughs to prevent or cure Alzheimer's disease.

We will define dementia generally as cognitive impairment that interferes with activities of daily living. Our definition is very different from the medical definition, which relies on brain pathology, for example, tau tangles or amyloid fibers to identify the existence of Alzheimer's. Although currently there are no treatments that can alter the pathology of the brain, if the criterion for an effective dementia intervention is whether a person can now follow a useful and productive lifestyle, then focusing on finding a reduction of symptoms can be a feasible dementia outcome that any intervention can seek to achieve.[2] Hence, the measures of dementia symptoms that we will employ in this paper will focus on cognitive functioning rather than brain pathology.

Since reducing dementia symptoms will now be the focus for judging an effective dementia intervention, it is important to be aware of how the dementia symptoms are to be measured. The instrument that is most comprehensive and conceptually valid is the Clinical Dementia Rating (CDR) scale, known as the *CDR® Dementia Staging Instrument* created by Washington University[3]. As an alternative, there is the Mini-Mental State Examination (MMSE)[4]. This is a much simpler instrument that is more widely used in practical settings.

Given that a number of evaluations of dementia interventions have been carried out, and shown to be socially worthwhile using cost-benefit analysis (CBA), based on the CDR scale, it is useful to know the extent to which the MMSE can be used as a suitable alternative for the CDR scale, to be used for future evaluations of interventions. In the medical literature, both the CDR scale and the MMSE have been viewed as measures of stages of dementia seriousness. For example, it is mainstream to class levels of dementia seriousness as there being pre-clinical dementia when there are no symptoms, mild cognitive impairment when there are some symptoms present, or dementia actually being present when symptoms are serious. In terms of staging, the MMSE has been shown to be a suitable surrogate[5].

However, when measures of dementia symptoms are going to be used for an evaluation of an intervention for a CBA, using dementia stages is much too broad to be useful. This is because a point or two reduction in symptoms, or even a half point reduction, can be the expected outcome, not a shift from one category to another. Therefore, the purpose of this paper is to explore the relationship between the two measures of dementia symptoms, to see the extent to which the MMSE empirically measures up to the CDR scale when undertaking a CBA.

The main analysis involves carrying out a regression analysis to estimate how a unit change in the MMSE converts to unit changes in the CDR. The estimation takes place using a large, national panel data set collected by the National Alzheimer's Coordinating Center (NACC) that contained both instruments, which is summarized below. The subsequent analysis seeks to validate the estimation of the conversion rate between the two instruments by carrying out a case study where a CBA of one intervention was undertaken using both instruments. In this way one can see the extent to which the CBA results using the MMSE can duplicate those found by employing the CDR scale, if one were to adopt the estimated conversion rate. In the next section we give an overview of the two instruments.

2. Overview of the two Dementia Symptoms Instruments

Our outline of the two instruments concentrates on how they are scored. As we have just explained, in the literature, the scores for the instruments are usually classified to indicate ranges for dementia symptoms that are to be regarded as normal, or questionable, or mild, or severe. Since we will be regressing one instrument on the other, we treat the two instruments as continuous variables and therefore ignore their use as measures of classifying dementia stages, which has been found to be problematic.[2]

2.1 CLINICAL DEMENTIA RATING SCALE.

The CDR is a measure of dementia severity used globally based primarily on a neurological exam and informant reporting. A CDR was administered to each NACC participant at each visit by a clinician. There are six domains in the CDR: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Each domain is assessed using a 0 to 3 interval (none, mild, moderate and severe) with a questionable response being scored as 0.5. The CDR-SB (the CDR sum of boxes) is the aggregate score across all six domains and this has a range of 0 to 18. Table 1, adapted from Tables in the literature, details the CDR domains and the scoring[1,6].

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Table 1 Clinical Dementia Rating Scale (CDR).

Impairment	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight	Consistently slight forgetfulness	Moderate loss; marked for recent events	Severe loss; new material rapidly lost	Severe loss; only fragments remain
Orientation	Fully orientated	Fully orientated except for time relationships	Orientated only for place at examination	Disorientated with time and place	Orientated to person only
Judgment and Problem Solving	Solves everyday problems; judgment good	Slight impairment in judgment	Moderate difficulty in Judgment	Severely impaired in judgment	Unable to make judgments, solve problems
Community Affairs	Independent function at usual level	Slight impairment in activities	Unable to function at all these activities	No pretense of independent function outside home	
Home and Hobbies Personal Care	Life and interests well maintained Fully capable of self-care	Interests slightly impaired	Mild but definite impairment Needs prompting	Only simple chores preserved Requires assistance in dressing, etc.	No significant function in home Requires much help

2.2 MINI-MENTAL STATE EXAMINATION

The MMSE is the most widely used measure of cognitive function in clinical practice worldwide[7]. It has been advocated by the National Institute for Health and Clinical Excellence (NICE) in the UK to be used for economic evaluations of dementia interventions[8]. The MMSE is a 11-question measure that tests five areas of cognitive functioning. The areas, and their maximum scores are: orientation (10 points), registration (3 points), attention and calculation (3 points), recall (3 points) and language (9 points). The total score from all the five areas has a maximum of 30 points. For the first four areas, only a vocal response is required. For the language area, reading, writing, and following commands is required. Table 2 provides a simplified version of the areas and questions based on the appendix in the original article which presented the MMSE[4].

Table 2 Mini-Mental State Examination.

Cognitive Function	Question	Maximum Score
Orientation	What is the: year, season, date, day, month?	5
	Where are we now: state, county, town, hospital, floor?	5
Registration	State 3 objects: Can you repeat the names of all 3?	3
Attention and Calculation	Can you count backwoods from 100 by 7s? (Score just the first 5); or can you spell the five-letter word "world" backwards.	5
Recall	Can you recall the 3 objects previously stated?	3
Language	When shown a watch and pencil. Can you name them?	2
	Can you repeat the words "No ifs, ands or buts?"	1
	Can you take a paper in your right hand, fold it in half and put it on the floor?	3
	Can you close your eyes?	1
	Can you write a sentence?	1
	Can you copy a complex polygon?	1

It is important to understand that the higher the MMSE score, the lower the presence of dementia symptoms. Thus. the MMSE is, unlike the CDR, an inverse measure of cognitive impairment. This means that we should expect the MMSE to be negatively related to the CDR.

3. Materials and methods.

In this section we lay out the foundations for the estimation of the relationship between the two dementia symptoms measures. We first present the regression estimation framework. There will be four regression variants according to the controls that will be included. We then describe the data set, define all the variables that are given in this data set that will be used in the regressions, and give the data summary for each variable.

3.1 THE ESTIMATION FRAMEWORK

Since we will be using Panel data for our estimation, the regression equation is set up as a two-way fixed effects model[9]. In such models, all variables usually have a subscript denoted by *it*, where *i* is an observation for an individual, and *t* is an observation for time, the year considered. In our case, what changes over time is the visit number to the NACC. Given that some individuals made more than one visit to a clinic per year, to preserve uniqueness, the time variable in our analysis is denoted by the visit number *v*. This means that each observation in our analysis will be denoted by *iv*.

The two-way fixed effects model is implemented by including in the regressions both a set of individual dummy variable intercepts α_i and a set of visit number

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dummy variables α_v. This allows the error term ε_{iv} to be an independent random variable. With the CDR as the dependent variable, the MMSE as the main independent variable, and the set of controls given by Z, the regression equation is represented by:

$$CDR_{iv} = \alpha_0 + \alpha_1 MMSE_{iv} + \alpha_Z Z_{iv} + \alpha_i + \alpha_v + \varepsilon_{iv} \quad (1)$$

where the α coefficients are the regression parameters to be estimated. From equation (1), α_1 is the coefficient of interest.

3.2 THE FOUR REGRESSION VARIANTS

The first regression is when no controls are used, other than the time invariant variables that are automatically controlled for when fixed effect models are applied to panel data. Since dementia is age related, the second regression seeks to determine the extent to which the relationship depends on age, and thus is different for varying levels of dementia seriousness. Then one needs to test whether the relationship can be expected to be different according to the nature of the particular dementia intervention that one is evaluating.

The fourth and final regression is based on the reality that many CBAs of dementia interventions rely on mortality as the outcome measure for the evaluation. This means that one also needs to see whether the relationship between the two measures is affected by how otherwise individuals with dementia are likely to die, separate from the intervention being evaluated. For the choice of mortality controls, we referred to the economics demographic literature[10,11,12,13]. We will only be discussing those mortality determinants that were found to be statistically significant.

3.3 THE DATA SOURCE

The data for the regressions come from the National Alzheimer's Coordinating Center. NACC has constructed a data set that has been operational since 2005. These data consist of demographic, clinical, diagnostic, and neuropsychological information on participants with normal cognition, mild cognitive impairment, and dementia who visited 32 US Alzheimer's Disease Centers (ADC). The data was collected by trained clinicians using structured interviews and objective test measures. Steps were undertaken to standardize the data across the ADCs and this is why the data set is referred to as the Uniform Data Set. This data set is fully explained elsewhere[14,15,16].

3. 4 DEFINITIONS OF THE VARIABLES AND THE DATA SUMMARY

The variables used in the four regression equations are listed in table 3, together with their definitions as they appear in the Uniform Data set.

Table 3 Definitions of all the regression variables.

Dementia Variables	**Description**
CDR-SB	Clinical Dementia Rating (CDR) Sum of Boxes (SB). Total CDR score based on Memory, Orientation, Judgement & Problem Solving, Community Affairs, Home & Hobbies, Personal Care, each of the six categories on a scale of 0 to 3.
MMSE	Mini-Mental State Examination. Total MMSE score based on five areas: Orientation, Memory, Attention and Calculation, Recall and Language. Patients score between 0 and 30.
Controls	
Z1: Age	Subjects age at time of visit.
Z2: Corrective lenses	If the subject usually wears corrective lenses, is the subject's vision functionally normal with corrective lenses? 1 = Yes; 0 = No, if any functional impairment exists (reduced ability to do everyday activities such as reading, watching television).
Z3: Medicare eligibility	Is the subject eligible for Medicare? Age ≥ 65 = 1; Age < 65 = 0.
Z4: Nursing home	The subject's type of residence. Is the subject's residence a skilled nursing facility / nursing home? 1 = Yes; 0 = No.
Z5: Depression	Geriatric Depression Scale (GDS); Total GDS score. Sum of the 1s for the 15 ingredients of the GDS scale, short form.
Z6: Height	Subject's height in inches.
Z7: Blood Pressure	Subject's blood pressure (sitting), systolic.
Visits	Set of dummy variables for visits at NACCs (1 to 12).

Table 4 supplies the data summary. The average dementia score using the CDR-SB measure was 3.00, and for the MMSE it was 26.43. Thus, the MMSE scores will always appear larger when using this dementia symptoms measure. This means that a one-point change in the score from a dementia intervention using the CDR-SB measure will have more economic significance than a one-point change for the MMSE.

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Table 4 Data summary (n = 63,514).

Variable	Mean	Standard Deviation	Minimum	Maximum
CDR-SB	1.98	3.16	0	18
MMSE	26.43	4.69	0	30
Z1: Age	74.92	9.58	20	106
Z2: Corrective lenses	0.95	0.21	0	1
Z3: Medicare eligibility	0.87	0.34	0	1
Z4: Nursing home	0.003	0.057	0	1
Z5: Depression	1.90	2.41	0	15
Z6: Height	65.46	4.00	37	84
Z7: Blood Pressure	133.41	18.42	0	15
Visits	3.00	2.10	1	12

The average age of the clients was 75 years. The clients typically made 3 visits to the NACC. As for the new dementia interventions that are the controls, 95% of the sample wore corrective lenses, 87% were eligible for Medicare, and 0.3% lived in nursing homes. There were only three health care variables that were found to be significant. In the sample, blood pressure was high, average height was low, and so was the level of depression.

4. Estimation Results

Table 5 presents the results for all four regressions. In all equations, the MMSE is significantly related to the CDR well below the 1% level. Without any controls, in regression 1, a unit change in the MMSE is associated with a 0.4 reduction in the CDR (α_1 = –-0.4170). With just age as a control, in regression 2, the association is almost identical (α_1 = –-0.4169). This is an important result, as dementia is very much age related and we would want any surrogate for the CDR to be valid for any older adult.

Also important is the result in regression 3 that, if the MMSE is going to be used to carry out a CBA to evaluate a new dementia intervention, the association was only slightly affected (α_1 = –-0.3975) when three past evaluated non-pharmacological dementia interventions were present as controls, which includes vision correction that is the intervention that we will be using in the case study. Finally, when we added the mortality controls in regression 4, the association did not change too much (α_1 = –-0.3716). Mortality is the main outcome variable that is used in many CBAs of dementia interventions. Thus, it is useful to know that the mortality controls also did not noticeably impact the estimation of the association between the MMSE and the CDR.

The conclusion therefore is that our estimation finds that the association between the two measures of dementia symptoms is of the order of 0.4, and this result is robust to the many controls that were applied in the regressions.

Table 5 Relation between CDR and MMSE with and without controls (p-values in brackets) †

Independent Variables††	(1)	(2)	(3)	(4)
MMSE (α_1)	–-0.4170*** (0.000)	–-0.4169*** (0.000)	–-0.3975*** (0.000)	–-0.3716*** (0.000)
Age		0.0142 (0.198)		
Vision Correction			–-0.0943*** (0.001)	–-0.0439 (0.141)
Medicaid Eligibility			–-0.2102*** (0.000)	–-0.2137*** (0.000)
Nursing Home			1.8985*** (0.000)	1.8506*** (0.000)
Depression				0.0211*** (0.000)
Height				–-0.0536*** (0.000)
Blood Pressure				–-0.0011*** (0.004)
Constant				15.3017*** (0.000)
No. of observations	96,006	96,006	72,195	63,514
No. of individuals	31,427	31,427	25,865	23,451
F-Test†††	6.37*** (0.000)	6.37*** (0.000)	6.09*** (0.000)	6.21*** (0.000)

† Significance levels on coefficients: *10%; **5%; ***1% .
†† All equations also include 11 of the 12 visit numbers.
††† The F-test is for the null that all the α_i are equal to zero.

5. Case study: A Cost-Benefit Analysis of vision correction using the MMSE

In the CBA of vision correction based on the CDR as the measure of symptoms, the outcome variable to be valued was a reduction in mortality from the corrective lenses[17]. A unit reduction in the CDR lowered the probability of dying by 0.0030. Since vision correction lowered the CDR by 0.1858 points, the product of the two produced the effect of vision correction on mortality, which was to lower the probability of dying by 0.0006.

To carry out a CBA, the mortality effect has to be valued in monetary terms to become the benefits, which can then be compared with the monetary costs, to ascertain whether the difference between the two, called the net-benefits, is positive or not. Only if the net-benefits of a dementia intervention are positive will it be judged to be socially worthwhile and therefore worth financing, irrespective of how cost-effective the intervention may be[18].

For the CBA of vision correction, the monetary valuation of the mortality gain was derived from the Value of a Statistical Life literature, VSL[19,20]. The VSL is determined by a person's labor risk-wage trade-off. The VSL estimate used in the vision correction CBA for an older adult was $3.27 million when discounted to be in the same time period as the costs (details of the calculations are given in Brent, 2022). Applying this valuation to the

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mortality reduction produced a benefit estimation of $1,823. With a lifetime cost of $765, the net-benefits of vision correction per person was positive at $1,058 with a benefit-cost ratio of 2.4.

We can adopt the same methodology to carry out the CBA of vision correction using the MMSE to replace the CDR as the dementia symptoms measure. A unit reduction in dementia (that is, the rise in the MMSE) lowers the probability of dying by 0.0038. With vision correction increasing the MMSE by 0.2311, the probability of dying is lowered by 0.0009. Multiplying this mortality gain by $3.27 million results in a benefit of $2,943. The net-benefit is now $2,178 per person with a benefit-cost ratio of 3.8.

When one uses the MMSE to evaluate vision correction, one obtains the same conclusion as was obtained by using the CDR, which is that vision correction is socially worthwhile and therefore its purchase is justified. As expected from our estimation of the relationship between the two measures of dementia, using the MMSE would produce a higher benefit amount. If we used our rough approximation of 0.4 to determine the CDR equivalent, the $2,943 benefit amount would reduce to $1,177. This of the same order of magnitude as the $1,823 benefit amount obtained using the more comprehensive CDR measure of dementia symptoms.

More specifically, the larger MMSE numbers produced a 50% larger mortality loss estimate, which is close to the 40% prediction from our statistical estimation of the relationship between the two measures.

6. Conclusion

A number of recent CBAs of non-pharmacological dementia interventions have been carried out that found that these interventions were both effective and socially worthwhile. For those evaluations, the CDR was used to measure dementia symptoms. Data on the CDR on a national basis was available at the National Alzheimer's Coordinating Centers and this was the source for the evaluations of the recent non-pharmacological dementia interventions. The CDR is the most reliable and valid instrument to measure dementia symptoms and it has become the international standard. However, it requires a considerable amount of data from both the patient and from an informant, and so is problematic if a well-informed caregiver is not available. Hence, there is the need for a time-saving, easy-to-use, and clinically familiar instrument that is more practical. The MMSE has been proposed to be this practical alternative.[5] The MMSE requires only 5-10 minutes to administer.[4]

While the MMSE has been found to be a suitable surrogate for the CDR as a staging instrument, for a CBA of dementia interventions one cannot expect any one intervention to have such a large effect that someone will move all the way from, say, full dementia, to having mild-cognitive impairment, or even no dementia symptoms. Thus, for CBA purposes, it is useful to know how the MMSE relates to the CDR when both instruments are measured as continuous measures of dementia symptoms. This paper seeks to estimate the relationship between these two instruments using the same NACC data set that was used to carry out the CBAs of the recent non-pharmacological dementia interventions. To provide one test of the validity of the association between the two instruments, a case study was carried out to see the extent to which the CBA results of a dementia intervention using the CDR, can be duplicated using the MMSE, when using the exact same methods and data set.

In the process, this paper serves to supply what has been called a "concurrent validation" of the MMSE as an assessment scale of dementia symptoms.[7] That is, the MMSE was used alongside a gold standard based assessment by a very well validated measure, which is the CDR scale, and shown to perform well. The assessment involved a CBA of vision correction as an intervention to reduce dementia symptoms. We find that multiplying a MMSE outcome measure by 0.4 will not only provide the required conversion to a CDR, it will also allow a monetary evaluation of a MMSE outcome to be obtained from existing CDR valuations to form a measure of MMSE benefits, in order that a CBA can be applied to any dementia intervention using the MMSE.

Conflict of Interest Statement: None

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