ORIGINAL RESEARCH

Linking the Mini-Mental State Examination, the Alzheimer's Disease Assessment Scale–Cognitive Subscale and the Severe Impairment Battery: evidence from individual participant data from five randomised clinical trials of donepezil

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ABSTRACT

Background The Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the Severe Impairment Battery (SIB) are widely used rating scales to assess cognition in Alzheimer's disease.
Objective To understand the correspondence between these rating scales, we aimed to examine the linkage of MMSE with the ADAS-Cog and SIB total and change scores.
Methods We used individual-level data on participants with Alzheimer's disease (n=2925) from five pivotal clinical trials of donepezil. Data were collected at baseline and scheduled visits for up to 6 months. We used equipercentile linking to identify the correspondence between simultaneous measurements of MMSE with ADAS-Cog, and SIB total and change ratings.
Findings Spearman's correlation coefficients were of strong magnitude between the MMSE total score and the ADAS-Cog (rs from −0.82 to −0.87; p<0.05) and SIB total scores (rs from 0.70 to 0.75; p<0.05). Weaker correlations between the change scores were observed between the MMSE change score and the ADAS-Cog (week 1: r=−0.11, p=0.18; rs thereafter: −0.28 to −0.45; p<0.05) and SIB change scores (rs from 0.31 to 0.44; p<0.05). Linking suggested that the MMSE total scores were sensitive to moderate and severe cognitive impairment levels. Despite weak to moderate correlations for the change scores, moderate change levels linked well, indicating ceiling and floor effects.
Conclusions The current results can be used in meta-analyses, data harmonisation and may contribute to increasing statistical power when pooling data from multiple sources.
Clinical implications The current study results help clinicians to understand these cognitive rating scale scores.

BACKGROUND

Alzheimer's disease is a chronic neurodegenerative disease characterised by the progressive deterioration of neurons and atrophy of brain tissue.[1] Onset is insidious and gradual, with initial cognitive impairment in short-term memory and with disease progression spreads to multiple cognitive domains (e.g., executive functions, attention, language) become impaired.[2] To assess the extent of cognitive impairment, various rating scales have been developed to evaluate cognitive functioning in research and clinical settings at different stages of the disease.

The most widely used cognitive rating scale is the Mini-Mental State Examination (MMSE), which was designed to screen for cognitive impairment in under 10 minutes. However, the MMSE lacks sensitivity to distinguish severe levels of impairment. Subsequently, the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) was developed as a comprehensive assessment of the extent of cognitive dysfunction in Alzheimer's disease.[3] Despite an administration time of approximately 40 minutes, it has become the gold standard to assess the efficacy of antidementia treatments in clinical trials.[4] For instance, a 4-point difference between the treatment and the placebo groups is considered clinically relevant,[5] at least in most Alzheimer's disease trials where symptomatology is moderate.[6] For populations in the advanced stages of the illness, the Severe Impairment Battery (SIB) was developed to address the cognitive and behavioural characteristics of severe dementia.[7] It has an administration time of around 30 minutes. There are design trade-offs between these scales, including administration time, and ceiling and floor effects (i.e., scales that measure the most severe cases lack sensitivity to differentiate moderate cases and vice versa).

Nonetheless, being able to convert between scale scores is often desirable, even a requirement. Research has demonstrated conversions between rating scales in schizophrenia,[8] depression,[9] panic disorder[10] and Alzheimer's disease.[11] [12] Prior studies linking rating scales in Alzheimer's disease have been informative but are restricted to cross-sectional information, do not link change scores, do not link MMSE and SIB scores and do not consider

learning effects from the first measure administered to the second. Nonetheless, there are benefits to converting measures.[12] First, most clinicians are probably used to the MMSE, therefore an explanation as to what scores the other rating scales (e.g., the SIB mean will be useful. Second, in meta-analyses two different rating scales often need to be transformed into a single common metric. Third, healthcare maintenance organisations frequently have information on different rating scales that could be harmonised for a single statistical analysis. Fourth, datasets with different scale ratings can be pooled to increase statistical power.

OBJECTIVE

In the current study, we aim to link the MMSE to the SIB and the ADAS-Cog based on five clinical trials of Alzheimer's disease.

Study selection and analysis

We obtained access to the individual-level participant data of all randomised controlled double-blinded trials of donepezil conducted by Eisai Co in which two or more of the cognitive scales of interest were administered simultaneously. Data access was provided following the submission of an a priori analytic plan and analysed via a secure internet cloud-based platform (http://www.clinicalstudydatarequest.com). We included trials in which patients with Alzheimer's disease were assessed with at least two of MMSE,[13] the SIB[14 15] and/or the ADAS-Cog.[3]

Measures

The following three measures were administered in the trials.

Mini-Mental State Examination

The MMSE is comprised of 20 items and takes between 5 and 10 min to administer. It consists of components of cognitive functioning (e.g., time-space orientation, short-term memory, attention, language and construction) that constitute a single underlying entity of cognitive functioning.[13] MMSE total scores range from 0 to 30, with lower scores representing a worse cognitive deficit.

Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is a neuropsychological index of the severity of the cognitive symptoms of dementia.[4] It is comprised of 11 tasks (word recall, word recognition, constructional praxis, orientation, naming objects and fingers, commands, ideational praxis, remembering test instruction, spoken language, word-finding, comprehension) that include both participant-completed and observer-based assessments. ADAS-Cog total scores range from 0 to 70, with higher scores representing a greater cognitive deficit.

The Severe Impairment Battery

The SIB consists of 40 one-step questions and commands, with a scale score of 100 points and nine aspects of cognitive functioning (social interaction, memory, orientation, language, attention, praxis, visuospatial ability, construction, orienting to name). SIB total scores may range from 0 to 100, with higher scores representing a lesser cognitive deficit.[14]

The MMSE was administered in every trial. In contrast, the ADAS-Cog and SIB assessments did not coincide in the same trial or week (table 1). Across the trials, the MMSE was administered before the ADAS-Cog and SIB, except at week 24 in one trial.[16]

Statistical analysis

At step one of the analysis, we presented the trial characteristics and demographics. At step two, we conducted linking of each available pair of ratings assessed at the same week (between the MMSE with the ADAS-Cog and then the MMSE with the SIB) with one exception. One trial[16] had screening rather than baseline SIB assessments (conducted within the 28±7 days before drug administration, median 22 days). Therefore, it so was used as a baseline appraisal to maximise the sample size and because there was no alternative treatment for Alzheimer's disease when the trials were conducted.

We computed Spearman's correlation coefficients and equipercentile linking. Although there are no agreed thresholds to interpret Spearman's correlation coefficient values, we follow prior guidelines and interpret the magnitude as weak (0.10–0.39), moderate (0.40–0.69) and strong (0.70–0.89).[17] We computed equipercentile linking to examine the extent to which it was possible to convert between the study measures at each time point. Prior studies of schizophrenia[18] and depression[9 19] have used equipercentile linking. Equipercentile linking is a statistical method to equate scores between two test scales. In short, the method ranks percentile scores between tests, and there is no independent or dependent variable. In this way, transformations between test scores are ascertained.[20] We analysed all trials collectively as a unique population rather than by trial to maximise the sample size and so attain robust linkage estimates. Finally, we took the median value from the equipercentile linking values across different measurement points to define the corresponding scores between the scales. We report cut-offs that link to mild (21-25), moderate (11-20), and severe (0-10)

Table 1 Trial characteristics of the analytic dataset

Authors	N	Sex	Mean age (SD)	Assessments available for linkage by visit	Trial inclusion criteria
Rogers and Friedhoff[29]	156	Male: 63 Female: 93	71.9 (7.4)	ADAS-Cog, MMSE 0, 1, 3, 6, 9, 12	MMSE: 10–26 CDR: 1 or 2
Rogers et al[23]	481	Male: 176 Female: 305	74.0 (7.6)	ADAS-Cog, MMSE 0, 3, 6, 9, 12	MMSE: 10–26 CDR: 1 or 2
Rogers et al[30]	473	Male: 180 Female: 293	73.5 (7.2)	ADAS-Cog, MMSE 0, 6, 12, 18, 24	MMSE: 10–26 CDR: 1 or 2
Black et al[16]	342	Male: 101 Female: 241	78.1 (7.6)	MMSE: 0 to 24 SIB: −1, 8, 16, 24	MMSE: 1–12 Modified Hachinski Ischemic Score: 6 or less Functional Assessment Staging: 6 or more
Farlow et al[24]	1444	Male: 539 Female: 905	74.2 (7.9)	MMSE, SIB 0, 6, 12, 18, 24	MMSE: 0–20 SIB: 90 or less Cornell Scale for Depression in Dementia score: under 12

Week −1 refers to the screening assessment that was 28±7 before the drug administration (mean 23.67 days).
ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; CDR, Clinical Dementia Rating; MMSE, Mini-mental State Examination; SIB, Severe Impairment Battery.

Table 2 Sample characteristics

Visit	MMSE-ADAS-Cog total scores				MMSE-SIB total scores			
Week	N	MMSE	ADAS-Cog	r	N	MMSE	SIB	r
Baseline	1102	19.33 (4.73)	26.69 (11.16)	−0.82	1785	12.01 (5.17)	72.68 (19.19)	0.70
Week 1	152	19.64 (5.34)	26.29 (10.88)	−0.86				
Week 3	597	20.06 (5.23)	24.57 (11.32)	−0.84				
Week 6	996	20.10 (5.39)	25.04 (11.38)	−0.85	1225	13.53 (5.46)	76.41 (18.78)	0.72
Week 9	562	20.35 (5.62)	24.87 (11.17)	−0.86				
Week 12	961	20.17 (5.62)	25.40 (11.88)	−0.86	1156	13.83 (5.72)	77.05 (18.78)	0.72
Week 18	381	19.45 (5.82)	26.31 (12.30)	−0.86	1095	13.82 (5.76)	77.47 (19.22)	0.72
Week 24	380	19.09 (6.05)	26.73 (12.98)	−0.87	1549	12.74 (6.16)	74.61 (21.60)	0.75

ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; r, Spearman's correlation coefficient; SIB, Severe Impairment Battery.

Visit	MMSE-ADAS-Cog total change scores				MMSE-SIB total change scores			
Week	N	MMSE	ADAS-Cog	r	N	MMSE	SIB	r
Week 1	149	0.69 (2.34)	−0.92 (3.68)	−0.11				
Week 3	594	0.76 (2.61)	−2.04 (4.31)	−0.28				
Week 6	991	0.74 (2.82)	−1.64 (4.65)	−0.28	1225	0.52 (2.35)	2.05 (7.07)	0.31
Week 9	560	0.98 (3.05)	−1.57 (4.70)	−0.32				
Week 12	957	0.76 (3.05)	−1.17 (5.11)	−0.36	1156	0.76 (2.76)	2.36 (7.72)	0.37
Week 18	380	0.06 (3.16)	−0.36 (5.31)	−0.39	1095	0.71 (2.94)	2.47 (8.74)	0.43
Week 24	379	−0.31 (3.35)	0.03 (5.76)	−0.45	1548	0.53 (3.08)	1.02 (10.42)	0.44

All r values were statistically significant (p<0.05), except the correlation at week 1 between the MMSE and ADAS-Cog where p=0.18. Spearman's correlation coefficient values may be interpreted as weak (0.10–0.39), moderate (0.40–0.69) and strong (0.70–0.89).
ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; N, the sample size that varies owing to different visit schedules across trials; r, Spearman's correlation coefficient; SIB, Severe Impairment Battery.

dementia on the MMSE.[21] In this way, different scores become interchangeable and comparable. Equipercentile linking was computed using the equate library[20] in R 3.6.2.[22]

Sensitivity analysis
We conducted sensitivity analysis precisely as above, but without the trial by Rogers *et al*[23] owing to 13 participants at one site, which violated the trial protocol.

FINDINGS
Trial characteristics
We identified four randomised placebo-controlled clinical trials and one trial[24] comparing random dose levels (of 10mg or 23mg of donepezil) cumulating in 2925 trial participants. Four participants were removed owing to missing information following the screening phase in one trial,[24] leaving 2921 trial participants with information in the dataset. Of the 2921 participants, 1110 participants had MMSE and ADAS-Cog scores and 1786 had MMSE and SIB scores. Hence, the analytic dataset consisted of 2896 trial participants (table 1). In addition, eight participants who contributed to the linkage between ADAS-Cog and MMSE total and one participant who contributed to the linkage between MMSE and SIB total did not contribute to change scores due to missing baseline assessments. The trial characteristics of the analytic dataset are summarised in table 1. There were 1059 (36.6%) males and 1837 (63.4%) females, with a mean age (SD) of 74.4 (7.8) years. Total and change rating scale score descriptive statistics are shown in table 2.

Equipercentile linking
Spearman's correlation coefficients between the MMSE and the ADAS-Cog total were statistically significant (p<0.05) and of large magnitude at all time points (r=−0.82 to −0.87; table 2). Equipercentile linking of the MMSE total scores with ADAS-Cog total scores was calculated. Across different time points, each 10 point increase on the MMSE total score corresponded to a decrease of approximately 20 on the ADAS-Cog total score (see figure 1A and the conversion table: online supplemental eTable 1). In general, one MMSE point was equivalent to two ADAS-Cog points. Spearman's correlation coefficient between the MMSE and the ADAS-Cog change scores was null at baseline (r=−0.11), but was statistically significant (p<0.05) for the remaining weeks with weak to moderate magnitude (range from r=−0.28 to r=−0.45; p<0.05; table 2). These lower correlations may partly reflect the inability of the MMSE change to capture severe cases of ADAS-Cog change. Equipercentile linking between the MMSE and the ADAS-Cog change scores showed slight fluctuations over time from −2 to 5 on the MMSE with floor and ceiling effects where change was under −3 and over 5 (see figure 1B and the conversion table: online supplemental eTable 2).

Spearman's correlation coefficients between the MMSE and the SIB scores were of strong magnitude for the total scores (range r=0.70–0.75; p values <0.05; table 2) and a moderate magnitude for the change scores (range r=0.31–0.45; p values <0.05; table 2). Each point increase in the range 0–6 on the MMSE total score corresponded to an increment of approximately 8 on the SIB total score; for MMSE total scores ranging from 7 to 11 each point increase was linked to 4–5 point increases on the SIB score; and for MMSE total scores ranging from 12 to 30, each point increase linked to 1–2 point increments on the SIB total (figure 2A, and conversion online supplemental eTable 3). Examination of the linkage between the MMSE and SIB total change scores showed consistent linkage over time for
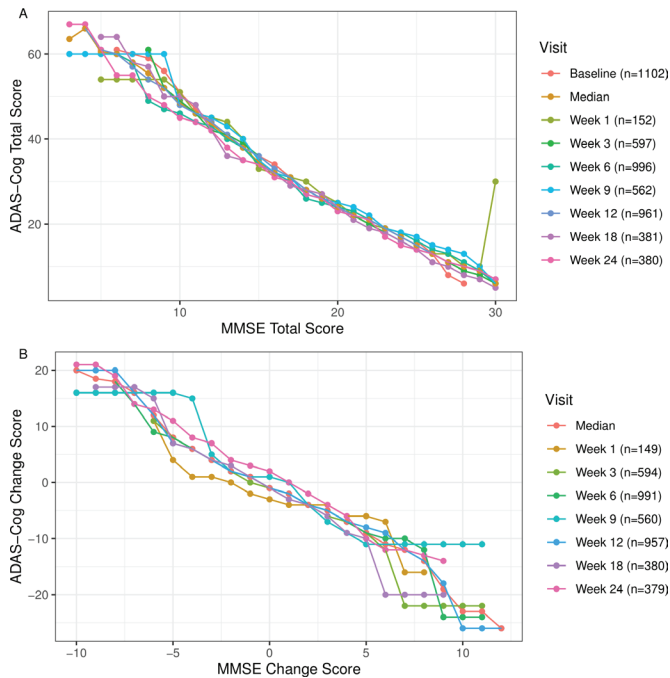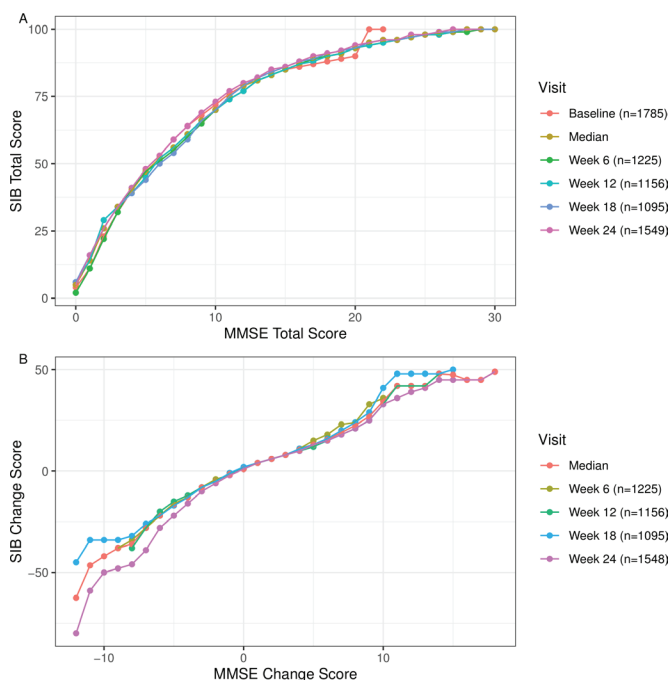
Figure 1 Linking the MMSE and ADAS-Cog scores. Fig. 1A shows the MMSE total score linked to the ADAS-Cog total score from baseline to week 24. Figure 1B shows the MMSE change score linked to the ADAS-Cog change score from week one to 24. ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination.

MMSE change scores ranging from −2 to 8 (and vice versa). MMSE total change scores under −3 to −9 generally linked to a point reduction of −4 on the SIB change score, with lower

Figure 2 Linking the MMSE and SIB scores. Figure 2A shows the MMSE total score linked to the SIB total score from baseline to week 24. Figure 2B shows the MMSE change score linked to the SIB change score to week six to 24. MMSE, Mini-Mental State Examination; SIB, Severe Impairment Battery.

Table 3 Conversion table between the study measures

Observed			Change		
MMSE	ADAS-Cog	SIB	MMSE	ADAS-Cog	SIB
0		5	−12		−62
1		14	−11		−46
2		26	−10	20	−42
3	64	34	−9	18	−38
4	66	40	−8	18	−36
5	60	47	−7	16	−28
6	60	52	−6	12	−22
7	58	56	−5	8	−16
8	56	61	−4	6	−13
9	52	66	−3	4	−8
10	48	70	−2	2	−5
11	46	75	−1	1	−2
12	44	79	0	−1	1
13	40	81	1	−2	4
14	38	83	2	−4	6
15	34	85	3	−5	8
16	32	87	4	−7	10
17	31	89	5	−9	13
18	28	90	6	−11	16
19	26	91	7	−12	19
20	24	93	8	−14	22
21	22	95	9	−19	27
22	21	96	10	−23	34
23	19	96	11	−23	42
24	17	97	12	−26	42
25	15	98	13		42
26	13	98	14		48
27	11	99	15		48
28	10	100	16		45
29	9	100	17		45
30	6	100	18		49

ADAS-Cog and SIB scores are based on median value across different measurement points to define the corresponding scores between the scales.
ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; SIB, Severe Impairment Battery.

values linking at −11 MMSE scores (see figure 2B, and conversion online supplemental eTable 4).

Table 3 summarises the corresponding scores across MMSE, ADAS-Cog and SIB. To interpret table 3, we used established guidelines to classify the MMSE scores into mild (21-25), moderate (11-20), and severe (0-10) dementia on the MMSE.[21] MMSE scores of mild dementia (i.e., 21–25) linked to ADAS-Cog scores from 15 to 22 and SIB scores from 95 to 98; moderate dementia (i.e., 11–20) linked to ADAS-Cog scores from 24 to 46 and SIB scores from 75 to 93 and severe dementia (i.e., 0–10) linked to ADAS-Cog scores over 48 and SIB scores under 70.

Sensitivity analysis by removing the trial by Rogers et al[23] owing to 13 participants at one site that violated the trial protocol did not manifestly impact the results (conversion online supplemental eTables 5 and 6).

Conclusions and clinical implications

The current study is the first linkage between the MMSE with ADAS-Cog and SIB total and change from baseline scores. The results show a generally consistent linking pattern over time and are easy to translate into practice. For instance, at baseline, an MMSE score of 10 was linked to an ADAS-Cog score of 48 and a SIB score of 70, and across time each 10 point increase on the

MMSE total score linked to a decrease of approximately 20 on the ADAS-Cog total score.

There are several potential reasons that the correlations between the total scores increased over time (see table 2). One explanation is that as the trial progressed, the variability of the scale scores increased and so did the correlation coefficients between them. Another possibility is that the natural progression of the disease induced an increase in generalised cognitive impairment. Furthermore, possibly repeated testing induced learning effects. Notably, the magnitudes of the change score correlations were less than that of the total scores, suggesting that conversion of change scores may be less reliable.[25]

Interestingly, the plots between the MMSE and the ADAS-Cog and SIB totals differ in form. The graph of the MMSE-SIB total linkage resembles an asymptotic function (i.e., SIB scores seem to level off at high MMSE scores). This likely reflects ceiling effects, namely, that the SIB is sensitive to severe stages but is insensitive to more normal range scores represented by MMSE scores of 25–30. The presence of ceiling effects was less evident on the linkage between the MMSE and the ADAS-Cog total scales.

There are several limitations to our study. First, as the results are based on clinical trial data with inclusion criteria, they may have restricted generalisability. Second, in one trial[16] ratings of the MMSE at screening were used because there were no baseline scores. Considering there were approximately 3 weeks between screening and baseline and the rate of deterioration in Alzheimer's disease, this artefact is unlikely to impact the study results. Third, the change scores did not correlate highly owing to outlying extreme scores. Fourth, we lacked item-level MMSE scores for a fine-level analysis. One might expect equivalence in well-defined domains of the same aspect of cognitive functioning. Fifth, the combined sample size and distribution did not enable us to analyse the placebo and donepezil groups separately. Sixth, we lacked information on the Montreal Cognitive Assessment (MoCA), which is a widely used measure to index cognitive impairment. Hence, the lack of information on the MoCA restricts the generalisability of the current results.[26] Seventh, MMSE was administered before the other rating scales, except for one trial where the SIB was administered before the MMSE.[16] This may raise concerns about the temporal order of each rating measure pair and learning cross-over effects between tests. However, at each visit, we consider learning effects are unlikely to adversely impact the result since the questions on the MMSE capture less severe impairment than the other rating scales.

A notable advantage of the current study was the large number of participants making the results robust. Moreover, all rating scale total scores were generally strongly correlated with each other, with little variability over time. This feature reinforces our faith in the robustness of linking functions.

In conclusion, our results provide linkages of the MMSE with the ADAS-Cog and SIB total and change scores often used in clinical trials of Alzheimer's disease.[27] The study results have the potential to contribute to clinical cross-walks when different clinicians use different scales and to meta-analytic calculations when researchers want to pool studies using different scales. Furthermore, our results can assist in data harmonisation and thus increase the statistical power of analyses that combine data from multiple sources. To facilitate the uptake of our results in practice, we have provided detailed conversion tables to directly link between rating scores of cognitive impairment in Alzheimer's disease. From a clinical point of view, individual priorities and goals of care will vary significantly depending on the stage of dementia, and discussions need to be tailored to the stage of illness. It is important, however, that complex decisions are discussed at a relatively early stage, when a person with dementia may be actively involved in care planning.[28]

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