Burden of central nervous system complications in sickle cell disease: A systematic review and meta-analysis

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Abstract
Sickle cell disease (SCD) patients are at high risk of central nervous system (CNS) complications and may experience significant morbidity. The study was conducted to describe the comprehensive burden of SCD-related CNS complications and to identify patient-reported outcome (PRO) instruments for future research. The review included 32 studies published from January 2000 to 2020, evaluating humanistic and economic outcomes. Twenty-three studies reported humanistic outcomes, 16 of which measured cognitive function using Wechsler Intelligence Scales. A meta-analysis was conducted, finding full-scale intelligence quotient (IQ) was significantly lower in: overt stroke versus controls: −12.6 (p < .001); silent cerebral infarct (SCI) versus controls: −5.7 (p < .001); overt stroke versus SCI: −9.4 (p = .008); and any event versus controls: −7.6 (p < .001). This review quantified the cognitive deficits associated with CNS complications in pediatric SCD populations and highlights the need for improved prevention/treatment. As PRO evidence was limited, we discussed areas for future research.

KEYWORDS
CNS complications, overt stroke, quality of life, sickle cell disease, silent cerebral infarct

1 | INTRODUCTION

Sickle cell disease (SCD) is a complex genetic blood disease involving multicell adhesion between red blood cells, white blood cells, platelets, and endothelial cells.1–3 An estimated 100,000 Americans suffer from this disease, many of whom are of African ancestry.4 SCD is a multi-system disorder with a range of acute and chronic clinical consequences driven by vaso-occlusion and hemolytic anemia. Vaso-occlusive crises, a hallmark of SCD, occur when circulation is obstructed by a buildup of sickled red blood cells and other cells. These crises are the primary cause of SCD hospitalization, cause ischemic damage resulting in severe pain, organ damage, decreased health-related quality of life (HRQoL), life-threatening complications, and early mortality.5,6 Common SCD-related complications include acute and chronic pain, acute chest syndrome, splenic sequestration, and vascular damage. Vascular damage may result in organ dysfunction affecting major organs like the heart, lungs, and brain; cerebrovascular events may increase the likelihood of serious central nervous system (CNS) complications.2,6 CNS complications in SCD range from blockage of small intracranial vessels to the narrowing of large blood vessels and subsequent neovascularization characteristic of moyamoya disease. Two well-described SCD-related CNS complications are overt strokes and silent cerebral infarcts (SCIs).7

Overt stroke is defined as a focal neurologic deficit of ischemic (75% of infarcts) or hemorrhagic type.7 In individuals with SCD, overt stroke

Abbreviations: CNS, central nervous system; CVA, cerebrovascular accident; FSIQ, full-scale IQ; HRQoL, health-related quality of life; HU, hydroxyurea; IQ, intelligence quotient; LOS, length of stay; MRI, magnetic resonance imaging; PerfO, performance outcome; PIQ, performance IQ; PRO, patient-reported outcome; QoL, quality of life; SCD, sickle cell disease; SCI, silent cerebral infarct; TCD, transcranial Doppler ultrasound; VIQ, verbal IQ; WISC, Wechsler Intelligence Scale for Children

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develops via a complex combination of one or more pathophysiologic defects, including low blood oxygen content, cerebral vasculopathy compromising cerebral blood flow, acute infection with fever, cardiovascular risk factors, prior cerebral infarcts, and a rapid decrease in hemoglobin levels. While effective screening (via transcranial Doppler ultrasound [TCD]) and prophylactic treatment (e.g., blood transfusion or hydroxyurea [HU]) can reduce the rate of overt stroke, without such treatment an estimated 11% of children with sickle cell anemia will experience overt stroke before age 19. In contrast, the prevalence of overt stroke in adults with SCD is 5.1%.

SCIs are magnetic resonance imaging (MRI)-detected brain lesions measuring at least 3 mm in their greatest linear dimension, visible in at least two planes of T2-weighted images without neurologic findings localized to the lesion. Although SCI often go undetected, they are thought to be far more common than overt stroke: a comprehensive screening study of newborns from the Créteil Pediatric Sickle Cell Referral Center in France indicates that 37% of children with sickle cell anemia will experience an SCI by the age of 14.

In addition to acute CNS complications, individuals with SCD have a shorter life expectancy (per simulation modeling) and in many respect an incommensurable disease burden. The availability of validated instruments to assess patients’ experiences is essential to understand the humanistic burden of complex manifestations of SCD, and to better assess interventions intended to improve patient quality of life (QoL). While existing literature suggests that QoL is poor in the general SCD population compared to unaffected individuals, the added burden of SCD-related CNS complications on QoL is not well understood. Moreover, given that both overt and silent strokes can cause cognitive deficits with multifaceted effects, an accurate, up-to-date understanding of the impact of these complications on intelligence quotient (IQ) and other subdomains of cognitive function is warranted. In light of the varied impacts of these cognitive deficits, in this systematic literature review we aim to synthesize the published evidence on the humanistic and economic burden associated with CNS complications in children and adults with SCD, as well as the patient-reported outcome (PRO) instruments used in this population. Kawadler and colleagues previously conducted an analysis of full-scale IQ (FSIQ) in children with SCD and stroke or SCI from 1980 to 2015; however, changes in disease management and education may affect IQ outcomes, and additional elements of IQ (performance [PIQ], verbal [VIQ]) were omitted.

2 | METHODS

2.1 | Systematic literature review methods

We performed literature searches on Embase, MEDLINE, and the Cochrane library (see Tables S1–S4). We limited our selected articles to English-language studies in a human population from January 2000 to May 2020. We also searched 11 congress abstract databases from the past 2 years. Duplicates were removed via an automated Excel function and a second round of manual reviewer deduplication.

Studies were included if relevant outcomes were reported for at least 15 individuals with SCD-related CNS complications, based on the rationale that studies with larger populations provide the strongest evidence. Both adult and pediatric studies were included in the review; however, due to a lack of adult IQ data, only pediatric studies were included in the meta-analysis. Studies only reporting outcomes for mixed populations (e.g., CNS complications and either SCD or thalassemia) were excluded, as were reviews and guidelines. Specific inclusion/exclusion PICOS criteria are outlined in Table S5. Relevant outcomes included humanistic or economic burden or PRO instruments employed in the population. Humanistic outcomes were broadly defined to include QoL, symptoms, and functioning. Economic burden was defined as direct and indirect costs including resource utilization and productivity loss. A PRISMA diagram showing the screening process is presented in Figure 1.

2.2 | IQ meta-analysis methods

As several studies reported cognitive function assessments using the same instrument, the Wechsler intelligence scales, a formal meta-analysis was performed. The objective of the meta-analysis was to calculate the mean difference in FSIQ, VIQ, and PIQ between children with SCD and overt stroke, SCD and SCI, and study controls.

Of the 32 studies included in the review, 10 studies were selected for inclusion in the meta-analysis based on the following criteria: reporting FSIQ, VIQ, and/or PIQ, based on either the third edition or an abbreviated version of a Wechsler intelligence test; pediatric populations with SCD, comparing IQ of an SCI group, overt stroke group, or both to a control group. Studies reporting results from the same cohort of individuals with SCI were excluded. Two studies recruited from the large nationwide Cooperative Study of Sickle Cell Disease roster, with one study recruiting individuals who reached age 6 by October 1, 1994 and the other recruiting individuals born between October 1978 and August 1988; some overlap of subjects between these studies is possible.

We assessed study heterogeneity among the articles, reviewing subject characteristics, subject sampling, nature of the control groups, identification of CNS complications, as well as study arm, complication, and outcome definitions.

2.2.1 | Statistical analysis

We evaluated the mean difference in FSIQ, VIQ, and PIQ across studies and compared these outcomes in the following groups:

1. Overt stroke versus SCI
2. Overt stroke versus control (SCD without CNS disease)
3. SCI versus control (SCD without CNS disease)
4. Any event (SCI/stroke) versus control (SCD without CNS disease)

In addition to the mean difference within each study, the absolute mean for each of three groups (overt stroke, SCI, and control [SCD without CNS disease]) was estimated. Given heterogeneity in study design and subject characteristics, the true effect size can be assumed to vary between studies. Therefore, we
used a random effects model with the three following groups: overt stroke, SCI, and control (SCD without CNS disease); the mean FSIQ, PIQ, and VIQ were estimated. Mean differences between groups were estimated and analyzed using random effects. For the comparison of any event versus control, a mixed effects model was used. First, the IQ results for within study groups of any event were calculated using sample-weighted combinations of SCI versus control and overt stroke versus control. Those within study sample-weighted IQ results were combined with a random effects model, to generate a comparison of any event versus control. This was done for the outcomes of FSIQ, PIQ, and VIQ.

All calculations were conducted using statistical software in R, using the mixmeta package. Significance of the mean difference was tested at the 95% significance level.

3 RESULTS

3.1 Systematic literature review results

In total, 31% of the included studies were retrospective observational (10 of 32 studies), 31% cross-sectional (10 studies), 28% prospective (9), and 9% randomized controlled trials (3). Study size varied widely from 16 to 4485 individuals with SCD and CNS complications. As shown in Figure 2, the largest studies estimated the economic burden of overt stroke, while the majority of smaller studies evaluated humanistic burden and performance measures in pediatric SCD populations. Most studies (81%) were conducted in the United States and the majority (75%) focused on children. Overt stroke (12 studies), stroke and SCI (10), or SCI only (7) were the most frequently described CNS complications.

Twenty-three studies reported humanistic burden, 16 of which measured cognitive function using the Wechsler intelligence scales. The mean FSIQ for SCD individuals with stroke was reported to be “extremely low” to “low average” (65.9–83.6); the mean FSIQ for SCD individuals with SCI was found to be “low” to “average” (77.2–95.9). Aggregate findings relating to FSIQ, VIQ, and PIQ are further explored in the meta-analysis. Apart from the impact of stroke/SCI, socio-environmental factors (i.e., low family income, lack of parent college education) were significantly associated with a decrease in IQ ($p = .005$ and .023, respectively).

Six studies assessed motor function, reporting significantly impaired function for individuals with stroke compared to
nonstroke SCD controls (Purdue Pegboard both hands: 7.5 vs. 10.1; \( p < .001 \)). Among children with SCD who had experienced a stroke, those receiving HU after one to four exchange blood transfusions for prevention of recurrent stroke had significantly less moderate-to-severe motor disability (physician assessed) than children not receiving HU (23.1% vs. 88.9%; \( p < .001 \)).

Nine studies reported economic outcomes related to health care resource utilization (8) and direct costs (5). Health care resource utilization for individuals with SCD who experienced an overt stroke was substantial, with an average length of stay (LOS) ranging from 2.5 to 9.2 days from included studies reporting LOS (all in the United States). Acute CNS complication management costs were also high, with median hospitalization charges of $18,956 (IQR 10,785–35,100 [2012 USD]) for individuals with SCD and stroke of all ages; $18,300 for children specifically. Preventive treatment costs were substantial in individuals with SCI, with annual transfusion plus chelation costs ranging between $18,149 and $67,361 (2016 USD). No studies reported indirect costs.

Studies included in the meta-analysis used IQ measurements that were assumed comparable. Wechsler Intelligence Scale for Children, Children’s Memory Scale, California Verbal Learning Test for Children, and the Trail Making Test.

### 3.2 | IQ meta-analysis results

#### 3.2.1 | Feasibility assessment

Of the 32 studies included in the review, 10 reported relevant IQ outcomes in pediatric individuals and were therefore included in the meta-analysis. Subject median age ranged between 8.2 and 13.9 years. Parent income and educational levels were reported in five of the studies, using a variety of measures. Parents of subjects in Brown et al. reported average annual household income that was below the national Black household averages at that time.

Individuals were recruited for the study via various methods, including referrals to a specific clinic, as well as multisite recruitment. Ghafuri et al. recruited subjects from individuals referred for evaluation of suspected developmental problems, while five other studies were conducted at sites in particularly low socioeconomic areas (as reflected in the low income and educational levels noted in the section above).

Studies included in the meta-analysis used IQ measurements that were assumed comparable. Wechsler Intelligence Scale for Children...
(WISC)-R and WISC version III were used for most children; some studies used Wechsler Abbreviated Scale of Intelligence (WASI), WISC version IV, and Wechsler Preschool and Primary Scale of Intelligence (WPPSI).

All studies contained a control group of individuals with SCD and either no evidence of cerebrovascular accident (CVA) or no evidence of SCI, as well as a group of individuals with SCI. Most, but not all, studies also included a group of individuals with overt stroke. The number of individuals in each comparison group is shown in Table 1.

Control groups for all studies were subjects without CNS complications with SCD; however, control groups were not genotype-matched with SCI/CVA subjects. Only one study also included controls without SCI/CVA; this non-SCD group was not included in this meta-analysis. Study controls were not related to the individuals with CNS complications, but were typically recruited from the same locality. Some studies attempted to recruit controls with similar demographic and/or socioeconomic background.

While there was some variance in definitions, SCI and absence of SCI/CVA were verified by review of brain MRIs in all studies except Ghafuri et al. and Steen et al. In these studies, absence of SCI/CVA was defined as no mention of cerebral infarcts in the subject’s medical records. An alternative analysis was therefore conducted excluding these two papers.

While there was heterogeneity between the remaining studies, particularly in terms of subject selection, these differences were assumed to be sufficiently minor, and representing random variations generalizable to the broad population of interest. Between-study variability was addressed by analyzing the mean difference between groups within each study as the main outcome.

### 3.2.2 Statistical analysis

Our meta-analysis found the mean FSIQ associated with stroke, SCI, and controls was 75.3 (95% CI: 63.4–87.3), 85.3 (95% CI: 76.4–94.3), and 89.4 (95% CI: 81.3–97.4), respectively. The mean VIQ associated with stroke, SCI, and controls was 81.6 (95% CI: 70.6–92.5), 83.9 (95% CI: 74.1–93.7), and 89.2 (95% CI: 79.7–98.8), respectively. The mean PIQ associated with stroke, SCI, and controls was 75.7 (95% CI: 64.6–86.7), 83.6 (95% CI: 73.8–93.3), and 87.6 (95% CI: 79.0–96.1), respectively.

The difference between stroke versus controls, SCI versus controls, stroke versus SCI, and SCI or stroke versus controls was statistically significant in all cases for FSIQ and PIQ, and significant for all comparisons except SCI versus stroke for VIQ (Figure 3). FSIQ scores were significantly lower in overt stroke versus controls: −12.6 (p < .001, 95% CI: −18.3 to −7.0), SCI versus controls: −5.7 (p < .001, 95% CI: −8.0 to −3.5), overt stroke versus SCI: −9.4 (p = .008, 95% CI: −16.4 to −2.5), and any event versus controls: −7.6 (p < .001, 95% CI: −11.2 to −3.9). VIQ scores were significantly lower in: overt stroke versus controls: −9.0 (p < .001, 95% CI: −12.9 to −5.1), SCI versus controls: −7.2 (p < .001, 95% CI: −9.8 to −4.6), and any event versus controls: −7.5 (p < .001, 95% CI: −10.8 to −4.1). Overt stroke versus SCI VIQ was also lower but not statistically significant: −4.4 (p = .08, 95% CI: −9.4 to +0.5). PIQ scores were significantly lower in overt stroke versus controls: −12.2 (p < .001, 95% CI: −16.2 to −8.2), SCI versus controls: −3.4 (p = 0.01, 95% CI: −6.0 to −0.8), overt stroke versus SCI: −8.0 (p < 0.001, 95% CI: −12.3 to −3.7), and any event versus controls: −7.4 (p < 0.001, 95% CI: −11.2 to −3.6). Consolidated baseline results outlining the mean difference in IQ for FSIQ, VIQ, and PIQ are presented in Figure 4 and Table 1.

An alternative analysis was conducted excluding studies with insufficient definition of overt stroke and/or SCI based on clinical opinion (Ghafuri et al. and Steen et al.). The mean difference between all comparisons except stroke versus SCI VIQ (as per the base case analysis) remained significantly negative. Consolidated results from this alternative analysis are presented in Table S6.

### 4 DISCUSSION

Our review and meta-analysis found that SCD individuals with CNS complications experience significantly decreased cognitive function and incur substantial health care costs compared to normal individuals and individuals with SCI without CNS disease. This burden is particularly noteworthy given that cognitive impairment may begin in childhood and can adversely affect many facets of life like education. Individuals with SCD are at a high risk for CNS complications despite decades of TCD screening, chronic transfusion therapy, and HU use. There is a clear need for additional treatment options to better address the humanistic and economic burden individuals with SCD-related CNS complications face.

In our review, we identified evidence of a substantial humanistic and economic burden associated with CNS complications in SCD. Specifically, individuals in this population frequently experience diminished cognitive function, have high health care resource utilization, and incur substantial treatment costs. Most studies evaluated humanistic burden or performance measures in a small pediatric SCD population with stroke and/or SCI. In contrast, the nine studies reporting economic burden included far larger populations, with all but one only assessing individuals with a history of overt stroke. The different sizes of studies evaluating economic and humanistic burden may reflect the challenge in measuring humanistic burden, partly due to the complexity of clinician-administered PerfoRs and the absence of PRO measures validated for this condition.

The Children’s Memory Scale and Trail Making Test, along with two iterations of the Wechsler scales, were identified instruments for cognition consistent with the American Society of Hematology and the U.S. Food and Drug Administration workshop recommendation for cognitive assessment in SCD clinical trials. While these measures provide useful insights into individual cognition, their length, complexity, and need for professional administration may limit their use to smaller populations. These limitations paired with a striking lack of research on QoL and productivity suggests PRO measures ought to be employed to assess the burden of disease more accurately.
| Meta-analysis                  | N   | IQ measure | Estimate | Standard error | p-Value | 95% CI lower bound | 95% CI upper bound | Q   | Q-p-value | I²   |
|-------------------------------|-----|-----------|----------|----------------|---------|-------------------|-------------------|-----|-----------|------|
| Stroke vs. no CNS             | 76 vs. 377 | FSIQ     | −12.63   | 2.87           | <.001   | −18.26            | −7.00             | 9.31 | .097      | 46.3%|
| SCI vs. no CNS                | 263 vs. 462 | FSIQ    | −5.74    | 1.15           | <.001   | −7.99             | −3.49             | 4.11 | .847      | 0.0% |
| Stroke vs. SCI                | 76 vs. 122 | FSIQ     | −9.43    | 3.54           | .008    | −16.37            | −2.49             | 11.02 | .051      | 54.6%|
| Any event vs. no CNS          | 198 vs. 377 | FSIQ    | −7.55    | 1.85           | <.001   | −11.18            | −3.93             | 1.92  | .860      | 0.0% |
| Stroke vs. no CNS             | 85 vs. 405 | VIQ      | −8.99    | 1.97           | <.001   | −12.86            | −5.13             | 4.26  | .512      | 0.0% |
| SCI vs. no CNS                | 156 vs. 447 | VIQ     | −7.19    | 1.33           | <.001   | −9.78             | −4.59             | 5.83  | .560      | 0.0% |
| Stroke vs. SCI                | 85 vs. 122 | VIQ      | −4.41    | 2.52           | .080    | −9.36             | 0.53              | 4.68  | .457      | 0.0% |
| Any event vs. no CNS          | 207 vs. 405 | VIQ     | −7.46    | 1.69           | <.001   | −10.78            | −4.13             | 2.19  | .822      | 0.0% |
| Stroke vs. no CNS             | 85 vs. 405 | PIQ      | −12.22   | 2.04           | <.001   | −16.22            | −8.23             | 5.97  | .309      | 16.3%|
| SCI vs. no CNS                | 156 vs. 447 | PIQ | −3.37    | 1.34           | .012    | −5.99             | −0.75             | 3.67  | .817      | 0.0% |
| Stroke vs. SCI                | 85 vs. 122 | PIQ      | −8.03    | 2.20           | <.001   | −12.35            | −3.72             | 3.55  | .616      | 0.0% |
| Any event vs. no CNS          | 207 vs. 405 | PIQ     | −7.43    | 1.93           | <.001   | −11.21            | −3.65             | 20.54 | .001      | 75.7%|

*Cochran’s Q: a measure of heterogeneity calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies.

*Statistic I²: the percentage of variation across studies that is due to heterogeneity rather than chance. Lower numbers indicate less heterogeneity.
Random effects models: A. stroke vs. control, B. SCI vs. control, C. stroke vs. SCI, D. any event vs. control

**FIGURE 3** Random effects models of mean difference in full-scale intelligence quotient (IQ) scores across four comparisons

Alternatively, novel computer-based cognitive research tools such as the Cambridge Automated Neuropsychological Testing Automated Battery could be employed. Not only could such PRO measures or automated batteries be employed in larger populations, but they could also help capture the all-encompassing nature of CNS complication-related deficits in cognitive function.

This study’s meta-analysis of IQ based on the Wechsler intelligence scales outlines differences in cognition in those with and without CNS complications. However, decreased cognitive function is a multifaceted issue with negative externalities (i.e., decreased productivity, increased caregiver burden) that are only partially captured by observing IQ. Indeed, youth with decreased cognitive function and SCD are at particular risk for experiencing a difficult transition into adulthood (i.e., problems learning to drive, managing finances, etc.), which in turn may lead to inadequate self-advocacy skills, socioeconomic hardship, and caregiver dependency. Moreover, a recent meta-analysis of the biological, environmental, and behavioral correlates of cognitive dysfunction in SCD found that patients with diminished cognitive function are significantly more likely to experience behavioral and emotional problems. While the Wechsler scales are a validated global measure of cognition, domain-specific measures such as the Trail Making Test can assess additional domains like executive function that are known to be impacted by SCD. Given the multifaceted aspects of cognitive function and available instruments, future research should assess cognitive domains that are relevant to individuals with SCD and choose instruments that are fit for purpose.

The findings from our review informed our decision to conduct an updated meta-analysis of IQ in individuals with SCD and CNS complications. IQ has been observed to change slowly over time (the Flynn effect), as has education, socioeconomic background, and disease management for SCD. Given these changes, restricting the analysis to studies post-2000 increases the reliability of the study relative to studies including older sources. The results of this meta-analysis (a 12.6-point decrease in FSIQ for stroke vs. controls, and a 5.7-point decrease in SCI vs. controls) align with results from Kawadler et al. (2016), and provide additional details. New findings include assessing VIQ and PIQ, and conducting additional assessments of stroke versus controls and any event versus controls.
This study is subject to similar methodological limitations as all reviews, namely, sensitivity of search terms to capture relevant studies, small population sizes of many included studies, and biases associated with included studies, such as publication bias. Some relevant studies of SCD patients may not have met selection criteria, specifically those requiring patients with CNS-related complications or requiring CNS-related outcomes. With 75% of included studies focusing exclusively on pediatric individuals, the generalizability of our results to adults may be limited. Indeed, key elements of burden may differ with age, and sparse data on nonstroke CNS complications (e.g., moyamoya disease) limit our findings. With all but three studies reporting exclusively on SCI and/or overt stroke, and no studies assessing either productivity loss or caregiver burden, these results suggest that substantial gaps remain in the published literature.

The meta-analysis was also subject to limitations. Control groups in the meta-analysis were individuals with SCD; it is possible that among controls, minor neurological damage was present at a rate above that of a non-SCD population, but not observed. The mean difference may thus be higher if compared to a general population; however, using non-SCD controls would probably have additional confounding variables and would therefore be less robust. Another similar limitation is that SCI would not have been measured in older studies or detected at a lower rate due to limited availability of CT/MRI scan. Also, retrospective claims database would not be able to capture SCI accurately. There were also differences between studies in characteristics that are known to affect IQ, such as median participant age and socioeconomic status. These confounding elements are partly eliminated when using results for mean difference between individuals within each study; however, according to clinical opinion mean difference may be slightly harder to detect at lower mean IQ values, suggesting the size of the mean difference could be underestimated.

Calculations of mean IQ should not be considered to reflect the general population of SCD individuals. Studies included in the analysis had subjects with lower income and concerning academic performance. Additionally, given historical misuse of IQ results (including as a method for discrimination), along with high representation of individuals of lower socioeconomic status among SCD individuals, and potential for cultural biases in the setting of IQ questions, results of mean IQ values should be interpreted with additional caution.

This study has revealed a number of concepts that merit further research. There is a need for PRO measures that capture the burden experienced by individuals with SCD and CNS complications, a historically underserved population. Measurement of PROs could greatly expand our understanding of how CNS complications affect cognitive function, in addition to other impacts on HRQoL, including activities of daily living, stigma, social and emotional functioning. Burden on caregivers is also important to investigate. Furthermore, the significant difference in FSIQ and PIQ between individuals with overt stroke and SCI suggests that future research is needed to understand how these distinct CNS complications may impact measures of cognitive function.

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Analyses were carried out by Soyon Lee, Sedge Lucas, and David Proudman. All authors participated in the conception and design of the study and the interpretation of data, and all approved the final manuscript for publication.
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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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