Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic form of cerebral small vessel disease (SVD) caused by mutations in the Notch3 gene, and it is associated with recurrent lacunar strokes and cognitive decline leading to dementia.1

Even before the onset of stroke and dementia, cognitive deficits are detected in patients with CADASIL,2 particularly in areas of attention, processing speed, and executive functions.2–5 Many studies have shown a similar pattern to older patients with sporadic SVD,6 although some studies have also shown early deficits in memory retrieval.3

Cognitive screening provides clinicians with important information about disease progression and cognitive disability as well as providing rapid measures for use in clinical trials. However, there are few targeted screening measures for SVD in general or, in particular, for patients with CADASIL where deficits may be subtle. Measures developed for cortical dementias such as the Mini-Mental State Examination7 and Alzheimer's Disease Assessment Scale-Cognitive Subscale test8 are relatively insensitive to subtle changes in key areas of function in SVD, namely executive function and information processing speed because of their lack of adequate measurement of these processes.6,9 An alternative is the Brief Memory and Executive Test (BMET),

Background and Purpose—Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a monogenic form of cerebral small vessel disease leading to early-onset stroke and dementia, with younger patients frequently showing subclinical deficits in cognition. At present, there are no targeted cognitive screening measures for this population. However, the Brief Memory and Executive Test (BMET) and the Montreal Cognitive Assessment (MoCA) have shown utility in detecting cognitive impairment in sporadic small vessel disease. This study assesses the BMET and the MoCA as clinical tools for detecting mild cognitive deficits in CADASIL.

Methods—Sixty-six prospectively recruited patients with CADASIL, and 66 matched controls completed the BMET, with a subset of these also completing the MoCA. Receiver operating characteristic curves were calculated to examine the sensitivity and specificity of clinical cutoffs for the detection of vascular cognitive impairment and reduced activities of daily living.

Results—Patients with CADASIL showed more cognitive impairment overall and were poorer on both executive/processing and memory indices of the BMET relative to controls. The BMET showed good accuracy in predicting vascular cognitive impairment (85% sensitivity and 84% specificity) and impaired instrumental activities of daily living (92% sensitivity and 77% specificity). The MoCA also showed good predictive validity for vascular cognitive impairment (80% sensitivity and 78% specificity) and instrumental activities of daily living (75% sensitivity and 76% specificity). The most important background predictor of vascular cognitive impairment was a history of stroke.

Conclusions—The results indicate that the BMET and the MoCA are clinically useful and sensitive screening measures for early cognitive impairment in patients with CADASIL. (Stroke. 2016;47:2482-2487. DOI: 10.1161/STROKEAHA.116.013761.)

Key Words: activities of daily living ■ CADASIL ■ cerebral small vessel disease ■ cognition ■ stroke
an open access brief screening tool specifically designed for the
detection of cognitive deficits in SVD,\textsuperscript{10,11} which has been exten-
sively validated in patients with sporadic SVD. The Montreal
Cognitive Assessment (MoCA) may also be a sensitive measure,
and it has been validated in a general stroke population\textsuperscript{12} and been
shown to be associated with subcortical white matter disease.\textsuperscript{13}

The primary aim of our study was to assess the use of the
BMET and the MoCA as a rapid screening tool for the detec-
tion of vascular cognitive impairment (VCI) and cognitive dis-
ability in CADASIL. The study also examines important risk
factors and background variables in relation to VCI.

\section*{Methods}

\subsection*{Participants}

Sixty-six patients (mean age=51.6, SD=9.5, range=34–70; sex:
male=38\%) with a genetically confirmed diagnosis of CADASIL,
based on a typical disease-causing cysteine altering mutation in the
\textit{Notch3} gene, were recruited prospectively from 2 national CADASIL
referral clinics at St. George’s Hospital, London, United Kingdom
and Addenbrooke’s Hospital, Cambridge, United Kingdom. None of
the patients had a clinical diagnosis of dementia. All had brain mag-
netic resonance imaging.

Five hundred and two healthy controls were recruited from family
doctor practices or other volunteer groups in South London as part
of the previous BMET validation study.\textsuperscript{11} Individuals with a history
of stroke, transient ischaemic attack, major central neurological or
major psychiatric disease were excluded. An age- and sex-matched
control population (n=66) were randomly selected from this larger
sample. Random sampling was conducted in $R$ (10$^7$ iterations) with
the probability of being selected weighted for sex. Controls older
than 70 (n=167) years were removed. There were 9 resultant samples
closely matching the CADASIL group for the age and sex ratio. A
random number generator then selected sample No. 6 from these
(age=mean=51.6, $D=9.0$, range=36–70; sex=male=36\%). Full details
of participant demographics are presented in Table 1.

\subsection*{Ethics}

Participants were recruited as part of studies approved by United
Kingdom National Health Service ethics committees. All participants
gave informed consent.

\subsection*{Cognitive Screening Measures}

The BMET is a fully normed screening test developed for the detec-
tion of VCI.\textsuperscript{10,11} It takes around 10 minutes to administer and con-
tains 4 items sensitive to executive dysfunction/processing speed: (1)
letter-number matching, (2) motor-sequencing, (3) letter-sequencing,
and (4) number-letter sequencing; and 4 items sensitive to memory
impairment: (1) orientation, (2) 5-item repetition, (3) 5-item recall,
and (4) 5-item recognition. Raw scores are converted into age-scaled
scores of 0, 1, or 2. The total BMET score is out of 16 with a cutoff
of $\leq$13 having previously been shown to indicate impairment.\textsuperscript{11} For
participants aged 34 to 39 years, aged 40 test norms were applied.

\begin{table}[h]
\centering
\caption{Participant Demographics and Neuropsychology Scores}
\begin{tabular}{|l|c|c|c|}
\hline
 & CADASIL (n=66) & Controls (n=66) & Comparison \\
\hline
Age (mean, SD, range) & 51.5, 9.4, 34–70 & 51.6, 9.0, 36–70 & $t(130)=-0.04$, $P=0.970$ \\
Sex (% male) & 37.9\% & 36.4\% & $X^2(1)=0.03$, $P=0.857$ \\
Ethnicity (% white, black, Asian, other) & 92.5\%, 1.5\%, 4.5\%, 1.5\% & 90.9\%, 3\%, 0\%, 6.1\% & $X^2(3)=5.1$, $P=0.162$ \\
NART FSIQ (mean, SD), n=56, 65 & 111.5, 8.5 & 119, 5.8 & $t(95.52^*)=-5.62$, $P<0.0001$ \\
Clinical stroke, % & 54.5 & 0 & n/a \\
White matter disease severity (Fazekas scale,† % $\geq 2$), n=58 & 95\% & n/a & n/a \\
Treated hypertension, % & 33.3\% & 18.2\% & $X^2(1)=3.94$, $P=0.047$ \\
Treated hypercholesterolaemia, % & 57.6\% & 10.6\% & $X^2(1)=32.40$, $P<0.0001$ \\
Diabetes mellitus, % & 3\% & 1.9\% & $X^2(1)=0.14$, $P=0.704$ \\
Smoking, % & & & \\
Never & 50.0 & 60.6 & $X^2(2)=0.98$, $P=0.612$ \\
Ex & 34.8 & 28.8 & \\
Current & 10.6 & 10.6 & \\
Not available & 4.5 & 0 & \\
BMET total score (mean, SD) & 12.4, 3.9 & 15.3, 1.2 & $t(76.78^*)=-5.76$, $P<0.0001$ \\
BMET executive/PS subscale (mean, SD) & 6.5, 2 & 7.8, 0.5 & $t(73.47^*)=-5.18$, $P<0.0001$ \\
BMET orient/mem subscale (mean, SD) & 5.9, 2.2 & 7.5, 0.9 & $t(85.66^*)=-5.34$, $P<0.0001$ \\
MoCA total score (mean, SD) n=30, 54 & 23.7, 5.5 & 27.4, 2 & $t(33.45^*)=-3.59$, $P<0.0001$ \\
IADL (% impaired) & 21\% & 0\% & $X^2(1)=18.40$, $P<0.0001$ \\
BADL (% impaired) & 27\% & 2\% & $X^2(1)=17.77$, $P<0.0001$ \\
\hline
\end{tabular}
\end{table}

BADL indicates Barthel Activities of Daily Living; BMET, Brief Memory and Executive Test; IADL, instrumental activities of daily living;
MoCA, Montreal Cognitive Assessment; NART_FSIQ, National Adult Reading Test Full-Scale Intelligence Quotient; PS, processing speed; and
orient/mem, orientation/memory subscale.

*df adjusted for Levene test for equality of variances.
†Adjusted Fazekas scale for white matter lesions 0 absent to 3 confluent.
Recent normative data for BMET can be found at http://www.bmet.info. Background interviews and testing were performed in 1 hour research windows to allow maximum participation of patients who were not local to the clinic location in which they were recruited and tested, also reflecting neurological clinic involvement. Where time was available, participants also completed other background measures and the MoCA (n=84). 13 The MoCA contains 8 sections developed to be relevant to mild cognitive impairment and validated in stroke: (1) visuospatial/executive, (2) naming, (3) memory, (4) attention, (5) language, (6) abstraction, (7) delayed recall, and (8) orientation. The MoCA has a clinical cutoff of <26.

Additional Measures
The National Adult Reading test (NART-R), 15 a measure of oral reading vocabulary and premorbid intelligence quotient (IQ; n=121); The Barthel Activities of Daily Living (BADL) scale, 16 a measure of general disability; and the instrumental activities of daily living (IADL), 17 a measure of cognitive disability (n=127).

Statistical Analysis
Demographic variables and cognitive test total scores were compared using t tests and χ² tests. To consider the impact of risk factors and background demographics on VCI status in CADASIL, we used Pearson χ² for categorical variables and Wald χ² for continuous variables. This was completed for both the MoCA and BMET diagnoses of VCI.

The sensitivity and specificity of the BMET and the MoCA clinical cutoffs for VCI detection was analyzed using receiver operating characteristic (ROC) curves. VCI status was determined using our predefined criteria: modified Petersen mild cognitive impairment threshold of a score of ≤1.5 SD from the control mean 14 on ≥4 BMET subtests. 10,11 To ensure that we did not inflate the effect of the BMET in predicting VCI, we included a second more stringent definition of VCI, which combined both the modified Petersen criteria and the MoCA clinical cutoff for cognitive impairment (<26). To allow for a comparison of the MoCA and BMET, the BMET ROC analysis was rerun in the cutoff for cognitive impairment (<26). To allow for a comparison and also clinical impairment on the BADL as defined in the study by general disability, we examined the association with BADL total scores indicating a lack of independence on any of the domains of the IADL. Reduced IADL was calculated as a score of −1.5 SD from the control mean 18 on ≥7 BADL items. To test this cutoff, also reflecting neurological clinic involvement. Where time was available, participants also completed other background measures and the MoCA (n=84). 13 The MoCA contains 8 sections developed to be relevant to mild cognitive impairment and validated in stroke: (1) visuospatial/executive, (2) naming, (3) memory, (4) attention, (5) language, (6) abstraction, (7) delayed recall, and (8) orientation. The MoCA has a clinical cutoff of <26.

Risk Factors and VCI
For VCI as diagnosed by the BMET, there were no significant effects of hypertension (χ²(1)=0.03, P=0.862), hyperlipidemia (χ²(1)=0.62, P=0.432), diabetes mellitus (χ²(1)=0.87, P=0.350), current smoking status (χ²(1)=0.127, P=0.722), ethnicity (χ²(3)=5.35, P=0.148), sex (χ²(1)=0.20, P=0.655), age (χ²(1)=0.005, P=0.946), or lesion load (χ²(2)=1.57, P=0.455). However, there was a significant effect of previous stroke (χ²(1)=7.52, P=0.006) and also premorbid IQ (χ²(1)=9.41, P=0.002) on VCI.

For the MoCA diagnosis of VCI, there were no significant effects of any risk factors or background variables: hypertension (χ²(1)=0.34, P=0.558), hyperlipidemia (χ²(1)=0.14, P=0.713), diabetes mellitus (χ²(1)=0.64, P=0.424), current smoking status (χ²(1)=0.006, P=0.936), ethnicity (χ²(2)=3.53, P=0.171), sex (χ²(1)=0.89, P=0.346), age (χ²(1)=0.382 P=0.537), lesion load (χ²(2)=3.07, P=0.215), or history of stroke (χ²(1)=0.362, P=0.547). Premorbid IQ approached significance (χ²(1)=2.90, P=0.089).

Markers of Disease and Cognitive Impairment
Post-hoc regression analyses were used to explore further the relationship between disease markers and cognitive impairment. These showed that a history of previous stroke was significantly associated with lower BMET total scores (β=−0.378, P=0.002), and this held when age was included in the model (β=−0.376, P=0.004). Fazekas score was not, however, associated with total BMET score (β=−0.091, P=0.496; with age included: β=0.052, P=0.737). The same analyses were carried out for the MoCA. This showed no significant association between a history of previous stroke and MoCA total score (β=−0.279, P=0.135; with age included in the model: β=−0.240, P=0.186). Fazekas score was not significantly associated with total MoCA score (β=−0.267, P=0.170; with age included in the model: β=−0.102, P=0.607).

Predicting VCI in CADASIL
On the basis of the modified Petersen criteria, as used in previous analyses, 10,11 VCI status was given to 24 of 66 patients with CADASIL and 2 of 66 controls. ROC curves were calculated to examine the detection of VCI using the BMET total score. ROC analysis including all participants calculated an area under the curve of 0.94 (95% CI, 0.87–1). A classification of cases based on a BMET cutoff of ≤13 indicated that this criterion had a sensitivity of 85% and specificity of 84% with a total predictive value (TPV) of 84%. This cutoff gave a good balance between sensitivity and specificity. Alternative cut-off points are presented in Table 2. When all controls were treated as unimpaired in the same analysis, a BMET cutoff of ≤13 had a sensitivity of 88% and specificity of 85% with a TPV of 84%.

Eighty-four participants (30 CADASIL, and 54 controls) had completed the MoCA. These data were used for a second analysis to examine the BMET and the MoCA’s prediction of VCI in parallel. For this subgroup of participants, ROC analysis of the BMET calculated an area under the curve of 0.95 (95% CI, 0.91–1). A classification of VCI cases based on the BMET cutoff of ≤13 gave 81% sensitivity and
Table 2. Alternative Clinical Cutoffs for the Prediction of VCI Using the BMET

<table>
<thead>
<tr>
<th>Score</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤11</td>
<td>69</td>
<td>99</td>
</tr>
<tr>
<td>≤12</td>
<td>81</td>
<td>90</td>
</tr>
<tr>
<td>≤13</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>≤14</td>
<td>92</td>
<td>79</td>
</tr>
</tbody>
</table>

Possible cut-off points indicated from the ROC analysis. ≤13 is the existing clinical cutoff for the BMET test. BMET indicates Brief Memory and Executive Test; ROC, receiver operating characteristic; and VCI, vascular cognitive impairment.

88% specificity, with a TPV of 87%. A ROC analysis of the MoCA calculated an area under the curve of 0.87 (95% CI, 0.77–0.97). A classification of VCI cases based on the MoCA clinical criterion of a score of <26 gave 81% sensitivity and 79% specificity, with a TPV of 81%. When all controls were treated as unimpaired using the same analysis, the BMET had a sensitivity of 80% and specificity of 87% with a TPV of 86%, and the MoCA had a sensitivity of 80% and a specificity of 78% with a TPV of 79%.

To avoid bias, adjusted criteria for VCI were created where the participant was defined as impaired if meeting both the original BMET criteria for VCI and the MoCA clinical criterion of <26. The ROC analysis for BMET calculated an area under the curve of 0.99 (95% CI, 0.99–1). A classification of VCI cases based on the BMET cutoff of ≤13 gave 100% sensitivity and 98% specificity, with a TPV of 99%. An ROC analysis of the MoCA calculated an area under the curve of 0.81 (95% CI, 0.67–93). A classification of VCI cases based on the MoCA clinical criterion of a score <26 gave 80% sensitivity and 83% specificity, with a TPV of 82%. When all controls were treated as unimpaired using the same analysis, the BMET had a sensitivity of 100% and specificity of 91% with a TPV of 93%, and the MoCA had a sensitivity of 87% and a specificity of 80% with a TPV of 81%. A summary of the predictive values are given in Table 3.

Table 3. Summary of Predictive Values in All Participants

<table>
<thead>
<tr>
<th>Screening Criteria</th>
<th>VCI Diagnostic Criteria</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMET ≤13</td>
<td>Modified Petersen criteria</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>BMET ≤13</td>
<td>Cognitive disability (IADL)</td>
<td>92</td>
<td>77</td>
</tr>
<tr>
<td>BMET ≤13*</td>
<td>Modified Petersen criteria plus MoCA &lt;26</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>MoCA &lt;26*</td>
<td>Modified Petersen criteria plus MoCA &lt;26</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>MoCA &lt;26*</td>
<td>Cognitive disability (IADL)</td>
<td>75</td>
<td>76</td>
</tr>
</tbody>
</table>

Predictive values of the BMET and MoCA clinical cutoffs where different criteria for VCI are used. The predictive values are based on all participants (CADASIL and controls) included in analyses. BMET indicates Brief Memory and Executive Test; CADASIL, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy; IADL, instrumental activities of daily living; MoCA, Montreal Cognitive Assessment; and VCI, vascular cognitive impairment.

*Analysis performed only on the subgroup who had completed both the BMET and the MoCA (n=84).

Premorbid IQ and VCI Prediction

Following the finding that premorbid IQ showed a relationship with cognitive test outcomes, we examined whether the addition of premorbid IQ to the screening test cutoffs improved predictive accuracy for VCI. Using discriminant function analyses and adding in premorbid IQ to predict VCI (Petersen criteria), we found that for the whole group sensitivity increased to 91% compared with 85% using the BMET alone and specificity remained the same at 84%. When we took only those participants completing both screening tests, we found that for the BMET plus IQ, sensitivity increased to 92% from 81% and specificity marginally increased to 89% from 88% compared with the BMET alone. Similarly, for the MoCA plus IQ, sensitivity increased to 92% from 81% and specificity increased to 84% from 79% compared with the MoCA alone.

Predicting Cognitive Disability:

Impaired Activities of Daily Living

Using IADL as a marker for cognitive disability, we re-examined the predictive validity of the BMET (n=127; CADASIL=61, controls=66) and the MoCA (n=79; CADASIL=25, controls=54). We found that 13 of 61 patients with CADASIL and 0 of 66 controls in the original sample had cognitive disability. Using ROC analysis to determine the BMET classification of patients with and without cognitive disability gave an area under the curve of 0.89 (95% CI, 0.78–1.0). The clinical cutoff of ≤13 predicted cognitive disability with a sensitivity of 92%, specificity of 77%, and a TPV of 79%. For the MoCa, the area under the curve was 0.78 (95% CI, 0.53–1.0). The clinical cutoff of <26 predicted cognitive disability with a sensitivity of 75%, specificity of 76%, and TPV of 76%.

For a validity check, we calculated regression models to consider whether the BMET and MoCa’s relationship with the activities of daily living were specific to cognitive disability or a consequence of more general disability in patients with CADASIL. The IADL, an index of cognitive disability, and the BADL, an index of general disability, were included in the models. We found that the BMET significantly predicted IADL (F=9.05, df=1, P>0.0001) but not BADL total scores (F=0.99, df=1, P=0.325); and that the MoCa similarly predicted IADL (F=5.63, df=1, P=0.026) but not BADL total scores (F=0.814, df=1, P=0.376), suggesting specificity to cognitive disability. An additional analysis taking clinical impairment as the outcome variable showed the same pattern of results for the BMET (IADL impairment: X2(1)=7.22, P=0.007; BADL impairment: X2(1)=0.714, P=0.495); the MoCA (IADL impairment: X2(1)=5.46, P=0.019; and the BADL impairment: X2(1)=0.053, P=0.818).

Discussion

Main Findings

On the basis of the modified Petersen criteria,10,11 cognitive impairment was found in 24 of 66 patients with CADASIL and 2 of 66 controls. Compared with age-matched controls, the CADASIL group showed a significant reduction in scores
Secondary Analyses

Exposing the subdomains of the BMET, significant deficits were seen in both executive functioning/processing speed and also memory. Although it is well established that many patients with CADASIL display deficits in executive functions and processing speed before the onset of dementia, memory deficits have been less commonly identified in previous studies. They may, however, be worthy of consideration in neuropsychological assessment of this population. Of note is that the distribution of magnetic resonance imaging white matter hyperintensities in CADASIL, although broadly similar to sporadic disease, has more prominent temporal lobe involvement.

Consideration of background variables and risk factors showed that CADASIL patients with a previous stroke were more likely to have a diagnosis of VCI on the BMET than those without. Furthermore, previous stroke predicted overall BMET score even when age was accounted for in the analysis. This is in line with previous research showing executive dysfunction and reduced processing speed of a similar magnitude to sporadic SVD for CADASIL cases with a history of stroke, and a recent study showed that incident dementia is associated with recurrent stroke in CADASIL. Fazekas score, however, did not show a significant association with cognitive outcomes on either scale. It is worth noting that this may be because of its relative insensitive to subtle changes in lesion extent, particularly in this population where 95% were graded as 2 or 3. This issue may be better explored in future studies using more quantitative measures of lesion load. Certainly, white matter disease has previously been shown to be associated with the MoCA when using diffusion tensor imaging to map microstructural damage. Furthermore, the strategic location of white matter damage has also been shown to be of importance when assessing the relationship between lesion and cognition in SVD. This information is not captured by Fazekas and therefore may add to its insensitivity. Future analyses may need to consider lesion locations in addition to extent.

Our secondary analyses also indicated a significant association between premorbid IQ and cognitive impairment on the BMET, with a borderline association with the MoCA. Premorbid IQ is thought to be associated with predisease neural organization, described as cognitive reserve. Although reserve in SVD is largely understudied, there is evidence that it might mitigate the relationship between white matter disease and cognitive impairment in normal aging and also in patients with CADASIL. Because of this potential influence on cognitive outcomes, we performed a further analysis where premorbid IQ was added into the predictive model for the detection of VCI. Our results showed that even with already high levels of prediction by the BMET and MoCA, the predictive value was further enhanced by the inclusion of premorbid IQ. This emphasises the importance of considering core background variables when performing cognitive screening in patients with SVD and also suggests a potentially fruitful avenue for future research projects looking at cognitive reserve in SVD.

It is acknowledged that these findings need further consideration in larger population. Furthermore, it is noted that the BMET is normed only from age 40 years, and that the use of these norms for those aged <40 (34–39) years may have reduced slightly the levels of impairment in the scores from this group. Furthermore, the lack of normative data for the MoCA may have also reduced its potential sensitivity. A future important direction for cognitive screening measures is their adaptability to younger population.
In conclusion, the results of this study demonstrate that a high frequency of cognitive impairment in nondemented patients with CADASIL and show that the BMET and the MoCA provide a sensitive and specific tools for detecting cognitive deficits in this population.

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Disclosures
None.

References
Brief Screening of Vascular Cognitive Impairment in Patients With Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy Without Dementia
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