The EXCITE Stroke Trial: Comparing Early and Delayed Constraint-Induced Movement Therapy

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Abstract

Background and Purpose—Although constraint-induced movement therapy (CIMT) has been shown to improve upper extremity function in stroke survivors at both early and late stages post-stroke, the comparison between participants within the same cohort but receiving the intervention at different time points has not been undertaken. Therefore, the purpose of this study was to compare functional improvements between stroke participants randomized to receive this intervention within 3–9 months (early group) to participants randomized upon recruitment to receive the identical intervention 15–21 months post-stroke (delayed group).

Methods—Two weeks of CIMT was delivered to participants immediately after randomization (early group) or one year later (delayed group). Evaluators blinded to group designation administered primary (Wolf Motor Function Test [WMFT], Motor Activity Log [MAL]) and secondary (Stroke Impact Scale [SIS]) outcome measures among the 106 early participants and 86 delayed participants prior to delivery of CIMT, two weeks thereafter and 4, 8 and 12 months later.

Results—While both groups showed significant improvements from pretreatment to 12 months post-treatment, the earlier CIMT group showed greater improvement than the delayed CIMT group in WMFT Performance Time and the MAL (P’s < .0001) as well as in Stroke Impact Scale Hand and Activities domains (P < .0009 and .0214, respectively). Early and delayed group comparison of scores on these measures 24 months after enrollment, showed no statistically significant differences between groups.

Conclusions—CIMT can be delivered to eligible patients 3 to 9 months or 15 to 21 months following stroke. Both patient groups achieved approximately the same level of significant arm motor function 24 months after enrollment.
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00057018

Keywords
stroke; upper extremity; constraint induced movement therapy; forced use; rehabilitation

Americans continue to experience more than 780,000 strokes each year with total costs for care and management estimated at $65.5 billion in 2008 and two thirds demonstrating impaired function in upper extremity usage.1 Rehabilitation regimens emphasize functional retraining for these stroke survivors2. Constraint-induced movement therapy (CIMT) requires restraint of the less impaired upper extremity (UE) through the use of a padded mitt that restricts hand usage and is coupled with behavioral training (repetitive and adaptive task practice) for up to 6 hours per day.3

The EXtremity Constraint Induced Therapy Evaluation (EXCITE) Trial was the first multisite randomized controlled study of a non-surgical or pharmacological procedure applied to patients 3–9 months post stroke.4 We found that, in comparison to a group receiving customary care only, those undergoing two weeks of CIMT showed significantly greater improvement5 that persisted through another follow up year.6 The control group subsequently was crossed over to receive CIMT one year after enrollment. In this paper we report the extent to which improvements in functional recovery following CIMT among this more chronic group(15–21 months post-stroke)would compare to those already reported for participants receiving CIMT within 3–9 months post-stroke.5

Patients and Methods

Study Population

Between January 2001 and January 2003, 222 participants were randomized to receive CIMT either at enrollment (earlier, E-CIMT, n= 106) or following a one year delay (delayed, D-CIMT, n =116). Participants were recruited if they had sustained a stroke 3–9 month prior to recruitment, could stand from a sitting position, could remain standing for at least 2 minutes without support and satisfied all inclusion criteria, including initiation of active extension of the wrist and fingers.4 Patients were excluded if they: were receiving or intended to receive pharmacological management of spasticity, had terminal diagnoses, were cognitively impaired, or intended to relocate. Specific joint passive ranges of motion and the Fugl-Meyer Upper Extremity Assessments, a commonly used 66 point scale to determine upper extremity synergy, were measured4, 7

CIMT Therapy

CIMT employs a padded safety mitt worn on the less-impaired upper extremity during 90% of waking hours over the 2-week CIMT training interval. Laboratory based training was performed over 10 consecutive days and consisted of 6 hours of monitored behavioral shaping and repetitive task practice, selected from over 60 tasks using only the impaired limb with the actual mean time of training within the laboratory. Actual training time increased with patient endurance, ranging from 1.5 hours on the first day to 4.5 hours on the last day.4 The mitt was only worn during the two week training interval following randomization (E-CIMT) or 1 year later (D-CIMT).

Adherence to mitt use was high in the laboratory environment and reinforced in the home through daily “homework”, behavioral contracts for both the patient and the caregiver, and a mitt compliance device that measured hand contact time within the mitt. The device was a contact plate that measured time of hand contact. The time output was continuously updated.
to a microprocessor housed within the mitt. The less affected limb was free to move to protect from loss of balance. During the training period, participants wore the mitt at home and the contact time was recorded and used as a surrogate for unimanual activity. Due to technical problems, the data are only available for a subset of participants undergoing training, but no differences between E-CIMT and D-CIMT groups were found.

Study Design

The EXCITE Trial was a masked cross-over design. After enrollment, the E-CIMT participants underwent 2 weeks of CIMT therapy (follow-up evaluations for 23.5 months). The D-CIMT participants received CIMT therapy after 12 months (follow-up evaluations for 11.5 months). D-CIMT participants could seek any rehabilitative therapy except CIMT during the treatment delay year after study enrollment. Information about these therapies was documented, but neither the quality nor the quantity was ascertained. All participants were administered primary outcome assessments every four months (baseline-Pre1; 0.5 month-Post1; 4 month; 8 month; 12 month-Pre2; 12.5 month-Post2; 16 month; 20 month; 24 month). Some measures were not administered at every visit.

Outcome Measures

**Wolf Motor Function Test (WMFT)**—The WMFT consists of 15 time-based and 2 strength items sequenced from requiring use of more proximal UE joints to more complex tasks requiring more UE joints and fine motor skills and allowing a maximum of 120 seconds per timed item completion. All items were videotaped and subsequently scored on a 6 point quality of movement scale, called the Functional Ability Scale, by trained raters masked to group assignment and session. This scale rates the task from not being initiated, through assistive use of the less impaired upper extremity to independent normal motion. Functional level refers to the amount of active wrist and finger extension demonstrated during three repetitions of active movement performed over one minute. Extension of all wrist and all digits by at least 20 degrees from a resting gravity–eliminated position or the ability to extend the wrist, thumb and two additional digits by 10 degrees over the same time interval defined higher and lower functional levels, respectively. Properties of the WMFT have been previously published.

**Motor Activity Log (MAL)**—The MAL is a structured interview containing 30 ADL (activities of daily living) items administered independently to participants who rated each item on an 11-point scale for Quality of Movement (QOM) and for Amount of Use (AOU) of the paretic limb. The MAL exhibits good convergent validity (r > .68) and has been validated with the Hand Function domain of the Stroke Impact Scale (SIS) and with accelerometry measurements.

**Stroke Impact Scale (SIS)**—The SIS, a secondary outcome measure, is a comprehensive, health status patient-report that measures changes in a summary measure and 8 sub-domains of impairment, function and quality of life, including strength, memory, emotion, communication, activities of daily living (ADLs), mobility, hand function, and participation.

**Defining Clinically Important Improvements**

Clinically important improvement was defined as a change in the number of WMFT tasks that could be completed (under 120 seconds) after CIMT treatment. A score of “3” or greater on both the QOM and AOU MAL provides the first indication of ADLs item initiation without use of the less impaired limb. Therefore, the change in number of MAL items that are rated ≥3 following CIMT was also assessed.
Statistical Analysis

The effects of CIMT on functional outcomes between E-CIMT and D-CIMT groups were compared in the year following treatment. An intent-to-treat plan was used so that all data were included in analyses. The main analysis was a mixed effects repeated measures (MERM) analysis (SAS PROC MIXED). Factors included treatment group (E-CIMT or D-CIMT), functional ability (high or low, based on active wrist and finger motion) as between-subject factors, and evaluation time point as a within-subject repeated measure variable. Least-squares means, used to ensure that missing values did not distort means and to incorporate covariate adjustments in the means, were computed for each separate evaluation for each group. The WMFT items are timed, with shorter times indicating better performance, and were analyzed using log transformed values (back-transformed values are presented for interpretability). For count variables, Poisson-link GEE models were used. Specific comparisons were tested using pre-planned contrasts. These included comparisons of pre-and post-treatment values (to assess treatment effect), pre-treatment to 12 months post-treatment values (to assess persistence of treatment), change from Pre1 to Pre2 for the D-CIMT group (to examine natural, non-specific changes), and difference between intervention and no-intervention intervals for the D-CIMT group. All queries were pre-specified and performed at the nominal significance level of $\alpha = .05$. A Bonferroni adjusted test was used to evaluate a posteriori comparisons and interactions between covariates (gender, concordance [agreement of hemiparetic upper extremity side with pre-stroke dominant side], and functional level), with a corrected p-value of $0.05/18 = .0028$. Statistical analyses were validated by last observation carried forward (LOCF) methods (results are equivalent and not presented).

Results

Study Population

At randomization, there were 106 E-CIMT (mean time post-stroke, 178±64 days and 116 D-CIMT (mean time post-stroke, 187±67 days) participants, 86 of whom received treatment. Participant loss is shown in the CONSORT diagram (Figure 1).

D-CIMT Prior Treatment

During the year following randomization, 24% (21/86) of D-CIMT participants received some form of therapy. There were no significant interactions for the WMFT ($p = .25$) or the MAL AOU ($p = .99$), or the MAL QOM ($p = .73$) between these D-CIMT subgroups. This “external treatment” factor was ignored for other analyses. D-CIMT participants showed significant improvement on the WMFT, MAL scores including the number of tasks scored as $\geq 3$, and the SIS Meaningful Activities and Typical Activities subscales (Tables 1 and 2, D-CIMT, Pre1 v Pre2). Collectively, these results suggest that D-CIMT participants experienced some recovery prior to receiving CIMT. Although 30 D-CIMT subjects withdrew from the EXCITE trial prior to the training period (Figure 1), there were no pre-randomization differences in any demographic variables measured between those who withdrew from the trial and those who started training (results not shown).

Within Group Improvements

Both groups improved significantly with treatment for primary outcome variables (Table 1, E-CIMT, Pre1 vs. Post1; D-CIMT, Pre2 vs. Post2). Similar improvements were seen 12 months post-treatment (Table 2, E-CIMT, Pre1 v Pre2; D-CIMT, Pre2 v 24 M). These improvements are shown graphically for the WMFT and the MAL AOU (Figures 2A, 2B) and indicate that D-CIMT participants can achieve a level comparable to E-CIMT participants. Differences post-training between values at time points were assessed between groups. These tests were not significant, indicating that only minor differences between groups occurred after training.
Tests comparing results for time points separately for each group were not significant using Bonferroni-corrected tests (results not shown).

**Between Group Differences**

There were no differences in patient demographics between groups when they were initially randomized. Several significant between-group differences were found between the E-CIMT Pre1 data and the D-CIMT Pre2 data (Table 1), including: log mean WMFT time, WMFT Functional ability, Weight, Grip, MAL scores including the number of tasks scored as ≥ 3, and the SIS Hand Function and ADL/IADL (Meaningful) subscales, reflecting improvement in function in the D-CIMT group over the year long delay.

Table 2 presents the least squares means for all primary and secondary outcome measures for the time points relative to the year of intervention. For the E-CIMT group, Pre1, Post1, and Pre2 values are shown, while comparable time points are shown for the D-CIMT group (4 month, 8 month, 16 month and 20 month values are omitted from the table for simplicity). The primary test of the null hypothesis of no difference over time between groups adjusted for functional level is also presented (Table 2, “Interaction”). This test compares the results 12 months post-baseline between groups while adjusting for the pre-training level. The WMFT (all components except Weight), MAL (all components), and the SIS 7 Hand Function domain all show a significant interaction, where E-CIMT demonstrates a larger improvement than D-CIMT. For the SIS Hand Function domain, the E-CIMT improved by 24.2(Pre2-Pre1) compared to 5.6 (24M-Pre2) for the delayed group (p<0.0001) and improvements for the E-CIMT group’s SIS 8 ADL/IADL were marginally significant (p = 0.0507). A subsequent analysis that examines differences between the groups 24 months after enrollment (Table 1, column 3) indicates no significant differences on the WMFT and both MAL measures. In the SIS hand function (7), ADL/IADL (8), and communication (4) domains, however, the E-CIMT group reports significantly higher function than the D-CIMT group (means for the E-CIMT group at 24 months are not shown).

No demographic or baseline characteristics predicted study withdrawal during the year following treatment. Withdrawal post-treatment was examined using logistic regression and for time to event (Cox regression). Using Bonferroni-corrected p-values, no predictor was significant for either method.

**Covariate analyses**

For three important variables (gender, concordance, and functional ability), the 3-way interactions between treatment, evaluation and covariate were examined for outcome variables. Using Bonferroni-corrected tests, one interaction was significant (functional level for Variable MAL QOM > 3; results not shown).

**Clinically Important Improvements**

The ability to successfully complete tasks in the WMFT and use the affected upper limb in everyday activities (rating of MAL items ≥ 3) was considered evidence of clinically important improvements (see Table 2). The E-CIMT condition showed larger improvements in WMFT completion (E-CIMT: -.89; D-CIMT: -.20), AOU/MAL ≥ 3 (E-CIMT: 26, D-CIMT: 8), and QOM/MAL ≥ 3 (E-CIMT: 28; D-CIMT: 8). All interactions are significant (Table 2), indicating that the change for the E-CIMT group is larger than that for the D-CIMT group.

**Safety**

Severe adverse events (SAEs) occurring during the first year were presented previously. From Pre 1 to Pre 2, E-CIMT participants experienced 2 deaths and 14 SAEs. During the Pre 2 to 24
month interval, D-CIMT participants sustained one death and 10 individual SAE hospitalizations (emphysema, internal bleeding, second stroke, cancer, congestive heart failure, subdural hematoma, hypertension, chest pain, hip arthroplasty, two fractures). None of those events was related to the intervention. In a generalized linear model that controlled for the repeated events within individuals, comparison of adverse event rates between groups showed no statistically significant difference (p = .58).

Discussion

Until now, there has been little to no level I evidence to inform the hypothesis that earlier CIMT is better than later. Indeed, evidence from other animal\textsuperscript{13} and human\textsuperscript{14} stroke studies suggest that limb rehabilitation within days of a stroke may be detrimental to recovery. Some studies indicate CIMT delivered to chronic stroke survivors resulted in far more substantial improvements than those seen in acute patients.\textsuperscript{15}

In the EXCITE Trial, patients responded favorably to CIMT. While both groups improved, those participants receiving treatment within 3–9 months post-stroke demonstrated significantly greater changes from immediately before to 12 months after treatment. This finding supports other studies showing that rehabilitation applied sooner during the recovery phase results in a faster rate of change;\textsuperscript{16} however, increasing CIMT from 2 to 3 hours per day applied within a few days after stroke does not necessarily produce superior outcomes.\textsuperscript{17} Functional improvements following CIMT have been associated with cortical plasticity as mapped using transcranial magnetic stimulation to motor cortex,\textsuperscript{18–20} fMRI,\textsuperscript{21, 22} including a subset of EXCITE participants,\textsuperscript{22} and MRI\textsuperscript{23} ; the extent to which the magnitude of reorganization is influenced by relative chronicity is under investigation. To date, structural reorganization associated with early training has been characterized by maintenance of the original focus of motor control (primary motor cortex); while training in the chronic phase was characterized by increases in bilateral sensory-motor, premotor and hippocampal activity\textsuperscript{23}. Recovery in the chronic state may be influenced by the loss of hand and expansion of non-hand representation areas within the primary motor cortex during the delayed period that contribute to atypical movement patterns and compete with subsequent neural reorganization during later training periods\textsuperscript{24}, resulting in smaller treatment effects in the chronic versus the acute periods\textsuperscript{25} as seen in this study.

The actual time to complete laboratory tasks (WMFT) and the perceived amount and quality of limb use in home based-activities (MAL) improved, as did the often neglected quality of life in hand function and ADL/IADL SIS domains. More significantly, the percentage of WMFT tasks that could be completed substantially improved in both groups (31% and 8%, E-CIMT and D-CIMT, respectively). Taken together with the percentage of real world activities that could be completed using the impaired limb independently (MAL>3)), both groups showed functionally meaningful gains but with a more profound improvement noted in the E-CIMT group. Similar to findings from our first year analyses,\textsuperscript{5} these chronicity effects were not affected by functional level (amount of active wrist and finger range of motion), concordance or gender.

The most apparent and likely biggest factor for the greater treatment effect in early vs. late is the discrepancy in when each group began the intervention. While a subset of D-CIMT received other interventions during the year prior to CIMT, this did not affect the amount by which they improved. The improvement seen in the D-CIMT group when exposed to CIMT one year later speaks to the potency of this approach but CIMT accounts for some, although not all, of this improvement. The possibility that the quarterly evaluation visits alone may have focused attention on paretic limb use during the no-training interval cannot be ruled out.
The D-CIMT group showed improvements during the year of no training as evidenced by pre-CIMT outcome measures that were actually better than Pre1 measures in the E-CIMT group (Figure 1). The magnitude by which this chronic group could improve after CIMT might well have been limited by: the extent of which they could improve or the extent to which our outcome measures were sensitive to improvements resulting from continued efforts to use the limb during the post-enrollment interval; changes in motivation; limitations in motor control caused by persistence or changes in muscle tone or strength; alterations in self-perception of the potential for limb use; or neuroplastic reorganization of the sort mentioned earlier. Furthermore, when considering the improvement by the D-CIMT group in the year prior to CIMT plus the year after CIMT (i.e., outcome 24 months after enrollment), D-CIMT outcomes on the WMFT and MAL are very similar to those for E-CIMT at the same time point. Therefore, while one can conclude from the data that CIMT produces improvement in motor measures that are greater when administered 3 to 9 months after stroke compared to one year later, our data also suggest that comparable results for both groups may occur after the full period of training and evaluation. In fact, both groups demonstrated significant gains at the end of their respective 10 sessions CIMT and then maintain these gains throughout the subsequent year.

Results from this trial and other investigations into the “signature” CIMT developed by Taub raise several issues. In addition to uncertainties about the optimal delivery and intensity of CIMT training, alternative forms of delivery using distributed rather than intense blocked practice models need to be explored. For example, small scale studies by Page and Wu offer the potential for comparable results with less intense individualized training. However, the optimal modification of CIMT needs to be defined first followed by a direct comparison to the present mode using a large enough sample size to undergo the rigors of an intention-to-treat analysis.

The results from this study show that the improvements persist, and none of the severe adverse events were related to CIMT. Yet the percent of stroke survivors who meet our inclusion criteria ranges from 5–23%, based upon how the degree of impairment is defined. Inevitably, the prospects for bolstering the value of this intervention for a larger population of patients may reside in better understanding of the causal and nonlinear relationships between limb function and daily use that will only emerge from proper translational research at both the theoretical and practical levels.

Acknowledgments

We express our profound appreciation to all the trainers and evaluators across the 7 participating EXCITE facilities for their diligence and commitment to excellence during this clinical trial which was funded by NIH Grant R01 HD37606 from the National Center for Medical Rehabilitation Research (National Institute of Child Health and Development) and from the National Institute of Neurological Diseases and Stroke.

References


Figure 1.
Consort diagram monitoring participants through the trial.
Figure 2.
A: Mean WMFT (seconds, s) and B: MAL AOU (amount of use, range: 0–5) scores, from enrollment through 24 months with E-CIMT receiving the intervention between 0 and .5 months following enrollment and D-CIMT receiving it one year after enrollment (between 12 and 12.5 months).
Table 1

Several tests for E-CIMT and D-CIMT

<table>
<thead>
<tr>
<th>Variable</th>
<th>E Pre1 v D Pre2</th>
<th>E-CIMT</th>
<th>D-CIMT</th>
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<tr>
<td>WMFT Mean Time</td>
<td>0.0015</td>
<td>0.0015</td>
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<td>WMFT Functional Ability</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<td>MAL QOM</td>
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<td>&lt;.0001</td>
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<td>MAL % QOM Tasks &gt; 3</td>
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<td>0.0296</td>
<td>&lt;.0001</td>
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<tr>
<td>SIS 4 Communicate W</td>
<td>0.3858</td>
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<tr>
<td>SIS 5 Typ Activity</td>
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<tr>
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<td>0.3581</td>
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Note: Author manuscript; available in PMC 2011 October 1.
Table 2
Effect of Constraint-Induced Movement Therapy on Primary and Secondary Outcome Measures

<table>
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<tr>
<th>Outcome Variable</th>
<th>E-CIMT</th>
<th>D-CIMT</th>
<th>Interaction</th>
<th>Within-cell StdDev</th>
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<tr>
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<td>Treatment</td>
<td>Post-Rx</td>
<td>Pre1 v Pre2</td>
<td>Treatment</td>
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<tr>
<td></td>
<td>Pre1</td>
<td>Post1</td>
<td>Pre2</td>
<td>p</td>
</tr>
<tr>
<td>Sample Size</td>
<td>105</td>
<td>98</td>
<td>80</td>
<td></td>
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<tr>
<td>WMFT mean time (sec)</td>
<td>30.0***</td>
<td>19.9***</td>
<td>21.1***</td>
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<tr>
<td>Functional Ability Scale score</td>
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<td>2.67</td>
<td>3.00</td>
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<tr>
<td>WMFT # Tasks &gt; 120</td>
<td>2.17</td>
<td>0.93**</td>
<td>1.13*</td>
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<td>MAL AOU</td>
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<td>MAL QOM</td>
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<td>2.25***</td>
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<tr>
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<td>45***</td>
<td>43***</td>
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<td>21***</td>
<td>48***</td>
<td>51***</td>
<td>&lt;.0001</td>
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<tr>
<td>SIS 4 Communicate W S</td>
<td>83.7</td>
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<td>&lt;.0001</td>
<td>58.6</td>
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</tbody>
</table>

P-values noted by significance symbols in the E-CIMT immediate ‘Post1’ and ‘Pre2’ columns compare groups at that time point controlling for pre-treatment values.

Symbol indicating significance -
* .01 < p <= .05;
** .001 < p <= .01;
*** p <= .001.

Analysis of WMFT time was performed using log values, but values in the original scale are presented to assist in interpretation. F values omitted to simplify table.

◆ Sample sizes for some measures differed slightly.