Chapter 6

Cross-education does not accelerate rehabilitation after an anterior cruciate ligament reconstruction: A randomized controlled clinical trial

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Abstract

**Background:** Sparse evidence suggests that cross-education affords clinical benefits in the early phase of anterior cruciate ligament (ACL) rehabilitation but it is unknown if such cross-education effects are reproducible and whether the early benefits are still present in later phases of rehabilitation. **Hypothesis:** Cross-education, as an adjuvant to standard therapy after ACL reconstruction, would improve self-reported and neuromuscular function up to 26 weeks after surgery by attenuating quadriceps weakness. **Study design:** Randomized controlled clinical trial. **Methods:** ACL reconstructed patients were randomized into a cross-education (n = 18) and standard care (n = 25) group. The cross-education group received standard care and performed additional leg press and leg extension exercises with the non-injured leg at an initial training load of ~400% of the reconstructed leg. The primary outcome was self-reported knee function (Hughston Clinic Knee questionnaire) and secondary outcomes were single- and multi-joint neuromuscular functions measured in both legs 29 ± 23 days prior to surgery and at 5, 12, and 26 weeks post-surgery. **Results:** Self-reported knee function decreased by 38% at 5 weeks post-surgery followed by an improvement, independent of cross-education, of 43% at 26 weeks post-surgery. Only 2 of 58 secondary outcomes revealed a cross-education effect, i.e., the quadriceps central activation ratio in the reconstructed leg showed less reduction at week 5 post-surgery but cross-education had a detrimental effect on dynamic balance in the non-injured leg at week 5, 12, and 26 post-surgery (all P ≤ 0.040). After 26 weeks of rehabilitation and relative to pre-surgery, the reconstructed leg improved maximal quadriceps (5-13%) and hamstring strength (8-9%), force control (24-34%), and dynamic balance (6%) (all P ≤ 0.043) and the non-injured leg improved maximal quadriceps (8-14%) and hamstring strength (7-18%), force control (22-34%), and dynamic balance (7%) (all P ≤ 0.031). Both groups did not improve in knee joint proprioception, static balance, and single leg hop distance. **Conclusion:** Twenty-six weeks of standard care improved self-reported knee function and neuromuscular function relative to pre-surgery but cross-education as an adjuvant to standard care did not further improve rehabilitation from ACL reconstruction.

**Keywords:** proprioception/balance, force accuracy, force variability, Hughston Clinic Knee score, maximal voluntary force, twitch interpolation
6.1 Introduction

Anterior cruciate ligament (ACL) reconstruction restores knee stability in the sagittal plane but quadriceps weakness persists [1]. This weakness is associated with poor hop test performance [2] and self-reported function [2,3]. Some [4-6] but not all studies [7] report that quadriceps weakness is present also in the contralateral non-injured leg up to 40 months after ACL surgery. Hence, exercising both legs after an ACL surgery might improve the outcome of rehabilitation [8].

Rehabilitation after ACL reconstruction has been recommended to consist of strength and neuromuscular training to minimize the risk of a second ACL injury [9]. Deleterious effects of great healing and open chain leg extensions are avoided in the early phase of ACL rehabilitation [10]. On the other hand however, disuse after 4-21 days of immobilization weakens the quadriceps by 10-47% [11,12]. Therefore, cross-education, which is the increase in motor output in a limb muscle after resistance training of the contralateral homologous limb muscle [13,14], might as an adjuvant to standard therapy, ameliorate the strength loss in the early phase after ACL reconstruction [15] and also reduce weakness in the non-operated leg [4-6]. Cross-education is also relevant to ACL rehabilitation because it acts through neural pathways that are involved in the strength loss [16]. Evidence for a strength-sparing effect produced by cross-education comes from immobilization studies in which strength training of the free limb attenuated strength loss and atrophy in the immobilized limb [17,18]. Neural mechanisms are likely to mediate such a strength-maintenance effect [18,19].

Cross-education studies in patients with unilateral orthopedic injuries are scant [15,20,21] but they all confirm that cross-education improves rehabilitation outcomes when added to standard care. To illustrate, ACL patients showed less quadriceps weakness [15] and better self-reported function [21] following additional eccentric strength training with the non-injured leg in the initial eight weeks after surgery. However, it is unclear if such cross-education effects are reproducible and the early benefits are still present in later phases of rehabilitation.

The present study examined if adding cross-education to standard care in the early phase of ACL rehabilitation could accelerate return to full capacity. Cross-education has been effective to increase muscle strength [13], neural activation [22], knee function [21], and range of motion [20] – deficits present in the leg recovering from an ACL surgery [9]. Therefore, we expected that ACL patients subjected to additional strength training
of the non-injured leg would show less loss of mobility as measured by the Hughston Clinic Knee (HCK) questionnaire (primary outcome) and less impaired neuromuscular performance (i.e., maximal quadriceps and hamstring strength, voluntary quadriceps activation, quadriceps force control, knee joint proprioception, single leg balance, and single leg hop distance).

6.2 Materials and Methods

6.2.1 Patients

Patients awaiting ACL reconstruction were recruited for 2 years from the Martini Hospital in Groningen, The Netherlands, under the direction of two orthopaedic surgeons. The patients who were scheduled for ACL surgery and met the inclusion criteria were invited to take part in the study. Inclusion criteria were: age between 18 and 60 years, unilateral ACL tear with/without partial meniscal resection, time between ACL injury and testing <2 year, autograft or allograft of any source, and minimal one supervised rehabilitation session per week. Patient exclusion criteria were: previous ACL reconstruction, history of a lower limb injury that required surgery, pregnancy, current or prior neurological conditions. The pre- and post-injury physical activity level was determined using the Tegner activity score [23]. Leg dominance was determined using the Waterloo Footedness questionnaire [24]. In accordance with the Declaration of Helsinki, all patients provided written informed consent to the experimental procedures, which were approved by the medical ethics committee of the University Medical Center Groningen (ID 2012.362).

6.2.2 Study design

Patients were randomly assigned to the standard care or cross-education group using a randomization plan. The rehabilitation protocol was standardized (Appendix 6.1) and similar for the two groups, except for unilateral quadriceps strengthening exercises (i.e., leg press, leg extension). The cross-education group performed these exercises with a low load for the operated leg and a high load for the non-injured leg. The initial training load for the non-injured leg was ~400% of the reconstructed leg and increased ~8% over time. The standard care group performed the exercises with low load and only with the reconstructed leg. Every patient was trained and supervised by one physiotherapist. Group allocation was completed after surgery but before the start of the rehabilitation program. Except for the physiotherapists, orthopaedic surgeons and all other researchers involved in testing were blinded to patients’ group assignment.
Testing was performed 29 ± 23 days prior to surgery and at 5, 12, and 26 weeks post-surgery. The primary outcome measure was self-reported knee function assessed with the HCK questionnaire [25]. The secondary outcome measures were maximal quadriceps and hamstring torque, quadriceps force control, knee joint proprioception, voluntary quadriceps activation, static and dynamic balance, and single leg hop distance. We assessed these secondary outcomes in each leg in one of nine random orders, with the starting leg being also randomly selected, and the randomization carried forward to subsequent testing sessions.

6.2.3 Self-reported knee function
The HCK questionnaire rates subjective knee complaints through answers marked on a visual analogue scale (0 to 100) to 28 questions [25]. These questions comprise symptoms of the knee, functioning in sports, and functioning in activities of daily living. The HCK questionnaire is reliable, valid, and sensitive to changes over time in ACL patients recovering from reconstructive surgery [25,26].

6.2.4 Maximal voluntary contraction (MVC)
Isometric and dynamic (eccentric 60°/s and concentric 60, 120, 180°/s) quadriceps and hamstring MVCs were measured on an isokinetic dynamometer (Biodex Medical Systems, Shirley, NY, USA) using an established protocol [7]. The peak torque, normalized to body weight, was used in the statistical analysis. The test-retest reliability of these measurements is good to excellent [27,28].

6.2.5 Voluntary quadriceps activation
Quadriceps activation was examined using the twitch interpolation technique and the central activation ratio (CAR) as detailed previously [7]. Ten patients experienced the electrical stimulation as unpleasant and therefore only a subsample of patients could be tested (standard care: n = 18; cross-education: n = 15).

6.2.6 Quadriceps force accuracy and variability
A target-matching task, with acceptable test-retest reliability [27,28], was performed with the target set to 20% MVC for isometric trials and to 40 Nm for dynamic trials [7]. After familiarization, patients performed three isometric trials at 65° of knee flexion (5-second duration) and four concentric and eccentric trials at 20°/s between 10° to 90° of knee flexion. Force accuracy was the absolute difference between the produced torque and the target torque. Force variability was the coefficient of variation (i.e., SD of the produced force divided by the mean force). Force control was calculated over the final 3-second portion of the data for isometric
trials and on the middle 2-second portion for concentric and eccentric trials. The mean across the trials was used in the statistical analyses.

6.2.7 Knee joint proprioception
We measured proprioception with a joint repositioning task at four randomized target positions (15°, 30°, 45°, and 60° of knee flexion) [27]. Knee joint proprioception was expressed in degrees as the absolute difference between the actual leg position and the target position. Test-retest reliability is acceptable [27].

6.2.8 Static balance
Static balance was tested with the one-leg standing balance test, starting with the eyes-open followed by the eyes-closed condition [29]. The maximum score that could be obtained was 60 seconds. The best score per condition was used in the statistical analysis. This test has acceptable test-retest reliability [29].

6.2.9 Dynamic balance
Dynamic balance was examined with the star-excursion balance test (SEBT) [30]. The SEBT was performed in clockwise direction and the starting line was randomly determined. The mean reaching distance was computed across the three trials, normalized to leg length, and the composite score, which is the average score across the eight lines, was used in the statistical analysis [7]. The other leg was measured after 5-minutes of rest. Test-retest reliability for the SEBT differed per direction from acceptable to excellent [31].

6.2.10 Single leg hop distance
The hop distance was examined in a subsample of patients (standard care: n = 18; cross-education: n = 13). Patients performed the single leg hop test for distance, allowing the arms to accelerate the jump [32]. Patients performed the test in their own sport shoes. The hop distance was measured from the toe at push-off to the heel where landed. The maximal hop distance of the two trials was used in the analysis. Test-retest reliability was excellent for the hop test [33].

6.2.11 Statistical analyses
Data in the text and figures are presented as mean ± SD. Normality was checked for each variable. The analyses were performed on log-transformed data for force accuracy and variability because normality was violated. We compared the two groups with a one-way ANOVA for group characteristics measured on a ratio scale and with a Kruskall-Wallis or chi-square test when measured on, respectively, an ordinal or
nominal scale.

The primary and secondary outcome measures were analyzed using multilevel analysis (SPSS version 23) because 12% of the data points were missing. In contrast to repeated measures analysis of variance, multilevel analysis handles incomplete data sets [34,35] and baseline differences between groups by allowing intercepts to vary between patients. We used a random intercept and slope model where repeated measurements (level 1) were nested within individual ACL patients (level 2). Thereafter, the following explanatory variables were added to the model: group (standard care, cross-education), time (pre-surgery, 5, 12, and 26 weeks post-surgery), and the group by time interaction. Gender was added as covariate for MVCs, voluntary quadriceps activation, and hop distance. The parameters of the multilevel model were estimated using the maximum likelihood method. Explanatory variables that significantly contributed to the model were subjected to a Bonferroni post hoc test to determine the means that were different. The level of significance (α) was set at P < 0.05.

Sample size calculation was performed using G*Power 3.1 [36]. We based our calculation on a 10-point difference in the primary outcome (i.e., HCK score) between the standard care and cross-education group. This difference was based on the scores obtained in a previous ACL study[26] and was considered to be clinically relevant. An SD of 14 points was used to calculate the effect size [26] Using an effect size of 0.36 with a power of 80% at the P < 0.05 significance level required a sample size of 42 (i.e., 21 patients per group). We aimed for 25 patients per group to allow for dropouts.

6.3 Results

Figure 6.1 shows the flow of patient enrolment (n = 57 enrolled) and Table 6.1 shows the group characteristics. In the 59 variables examined, only two revealed a cross-education effect.

6.3.1 Primary outcome

Figure 6.2 shows the time main effect for the HCK score ($F_{3,121} = 67.5, P < 0.001$). Post hoc testing revealed that self-reported knee function, relative to pre-surgery, was 38% worse five weeks post-surgery and 43% improved 26 weeks post-surgery (both $P < 0.001$).

6.3.2 Secondary outcomes

Maximal leg strength. Table 6.2 shows the quadriceps MVCs in the ACL reconstruction after ACL reconstruction.
patients’ reconstructed and non-injured leg. There was a main effect of time in each leg for all MVCs (all $P < 0.001$) except eccentric MVCs of the reconstructed leg ($P = 0.518$). Compared to pre-surgery, quadriceps MVCs of the reconstructed leg initially showed a 14-38% deficit 5 and 12 weeks post-surgery followed by a 5-13% improvement at 26 weeks post-surgery (all $P ≤ 0.022$). MVCs of the non-injured leg improved up to 14% over time relative to pre-surgery (all $P < 0.001$).

Appendix 6.2 shows the hamstring MVCs in the ACL patients’ reconstructed and non-injured leg. All hamstring MVCs revealed a main effect of time (all $P ≤ 0.036$) except eccentric MVCs of the reconstructed leg ($P = 0.155$). Relative to pre-surgery, a 21-43% deficit was observed in the reconstructed leg 5 and 12 weeks post-surgery followed by a 8-9% improvement at 26 weeks post-surgery (all $P ≤ 0.043$). Hamstring MVCs of the non-injured leg showed improvements of 7-18% over time compared to pre-surgery (all $P ≤ 0.031$).
## Table 6.1 | Group characteristics (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Standard care (N = 25)</th>
<th>Standard care + XED (N = 18)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28 ± 9</td>
<td>29 ± 10</td>
<td>0.801</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>11/14</td>
<td>13/5</td>
<td>0.066</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>75 ± 11</td>
<td>82 ± 13</td>
<td>0.053</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 ± 7</td>
<td>183 ± 7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 ± 3.3</td>
<td>24.5 ± 3.3</td>
<td>0.879</td>
</tr>
<tr>
<td>Leg dominance (left/right)</td>
<td>3/22</td>
<td>3/15</td>
<td>0.663</td>
</tr>
<tr>
<td>Operated leg (left/right)</td>
<td>8/17</td>
<td>8/10</td>
<td>0.405</td>
</tr>
<tr>
<td>Graft type (hamstring tendon/bone-pattellar tendon-bone/artificial)</td>
<td>21/4/0</td>
<td>16/1/1</td>
<td>0.301</td>
</tr>
<tr>
<td>Tegner score pre-injury</td>
<td>8 ± 2</td>
<td>8 ± 2</td>
<td>0.878</td>
</tr>
<tr>
<td>Tegner score post-injury</td>
<td>4 ± 1</td>
<td>4 ± 1</td>
<td>0.580</td>
</tr>
<tr>
<td>Number of training sessions</td>
<td>48 ± 13</td>
<td>45 ± 10</td>
<td>0.359</td>
</tr>
<tr>
<td>Time between injury and testing (days)</td>
<td>160 ± 89</td>
<td>196 ± 151</td>
<td>0.336</td>
</tr>
<tr>
<td>Time between testing and surgery (days)</td>
<td>30 ± 20</td>
<td>28 ± 28</td>
<td>0.762</td>
</tr>
</tbody>
</table>

XED, cross-education; *, group difference (P < 0.05)

**Figure 6.2** | The Hughston Clinic Knee score of the standard care (filled symbols) and cross-education group (XED) (open symbols). A higher scores means worse self-reported knee function. Scores at 5 and 26 weeks post-surgery were different vs. pre-surgery (P < 0.05). Note the non-significant but higher scores for the cross-education group at 5 and 12 weeks post-surgery were not related to a specific category of questions.
### Table 6.2 | Maximal quadriceps torque of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Pre-surgery</th>
<th>post-surgery</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>5 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td><strong>ACL reconstructed leg (Nm/kg)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eccentric 60°/s</td>
<td>Standard care</td>
<td>3.0 ± 0.8</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>3.6 ± 1.0</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>3.2 ± 0.9</td>
<td>——</td>
</tr>
<tr>
<td>Isometric</td>
<td>Standard care</td>
<td>3.0 ± 0.8</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>3.4 ± 0.8</td>
<td>2.0 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>3.2 ± 0.8</td>
<td>2.0 ± 0.8†</td>
</tr>
<tr>
<td>Concentric 60°/s</td>
<td>Standard care</td>
<td>2.1 ± 0.5</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>2.3 ± 0.8</td>
<td>——</td>
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<tr>
<td></td>
<td>Combined</td>
<td>2.2 ± 0.6</td>
<td>——</td>
</tr>
<tr>
<td>Concentric 120°/s</td>
<td>Standard care</td>
<td>1.8 ± 0.4</td>
<td>——</td>
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<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.9 ± 0.8</td>
<td>——</td>
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<tr>
<td></td>
<td>Combined</td>
<td>1.9 ± 0.6</td>
<td>——</td>
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<tr>
<td>Concentric 180°/s</td>
<td>Standard care</td>
<td>1.6 ± 0.4</td>
<td>——</td>
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<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.6 ± 0.7</td>
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<tr>
<td></td>
<td>Combined</td>
<td>1.6 ± 0.5</td>
<td>——</td>
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<tr>
<td>Variables</td>
<td>Group</td>
<td>Pre-surgery</td>
<td>post-surgery</td>
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<td></td>
<td></td>
<td>5 weeks</td>
<td>12 weeks</td>
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<tr>
<td>Non-injured leg (Nm/kg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eccentric 60°/s</td>
<td>Standard care</td>
<td>3.4 ± 0.9</td>
<td>3.9 ± 1.0</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>3.9 ± 0.8</td>
<td>3.9 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>3.6 ± 0.9</td>
<td>3.9 ± 1.1†</td>
</tr>
<tr>
<td>Isometric</td>
<td>Standard care</td>
<td>3.5 ± 0.8</td>
<td>3.6 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>3.7 ± 0.7</td>
<td>3.8 ± 0.7</td>
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<tr>
<td></td>
<td>Combined</td>
<td>3.6 ± 0.7</td>
<td>3.7 ± 0.8†</td>
</tr>
<tr>
<td>Concentric 60°/s</td>
<td>Standard care</td>
<td>2.5 ± 0.5</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>2.6 ± 0.7</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>2.5 ± 0.6</td>
<td>2.7 ± 0.6†</td>
</tr>
<tr>
<td>Concentric 120°/s</td>
<td>Standard care</td>
<td>2.1 ± 0.5</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>2.2 ± 0.6</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>2.1 ± 0.6</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Concentric 180°/s</td>
<td>Standard care</td>
<td>1.9 ± 0.5</td>
<td>2.0 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.9 ± 0.5</td>
<td>2.0 ± 0.5†</td>
</tr>
</tbody>
</table>

XED, cross-education; †, different compared to pre-surgery (P < 0.05)
**Voluntary quadriceps activation.** Figure 6.3 illustrates the group by time interaction for the CAR in the ACL patients’ reconstructed leg \( (F_{3,84} = 2.9, P = 0.040) \). The absolute decrease in CAR from pre-surgery to 5 weeks post-surgery was 5.7% more for the standard care vs. cross-education group, approaching significance \( (P = 0.054) \). The other measures of voluntary quadriceps activation are shown in Appendix 6.3. Time effects were only observed for the reconstructed leg \( (P < 0.001) \). Post hoc testing revealed impairments 5 and 12 weeks post-surgery relative to pre-surgery but the voluntary activation ratio showed improvements \( (all P \leq 0.019) \). These improvements do not reflect better quadriceps activation but are just the result of a smaller difference between the estimated and real MVC and an increased slope.

**Figure 6.3** | The central activation ratio of the quadriceps measured in the reconstructed leg \( (A) \) and non-injured leg \( (B) \). **Filled and open symbols, respectively, represent the standard care and the cross-education group (XED).** *, borderline significant difference between groups \( (P = 0.054) \).
**Force accuracy and variability.** Appendix 6.4 shows the force accuracy and variability in the reconstructed and non-injured leg. Main effects for time were observed (all $P \leq 0.039$). Force accuracy and variability in both legs improved 13-56% over time relative to pre-surgery (all $P \leq 0.024$).

**Knee joint proprioception.** Appendix 6.5 shows the knee joint proprioception of the ACL patients’ reconstructed and non-injured leg. A time effect was observed for the non-injured leg at a target angle of 60° ($F_{3,123} = 4.3$, $P = 0.006$).

**Multi-joint neuromuscular function.** Table 6.3 shows the multi-joint neuromuscular functions of the ACL patients’ reconstructed and non-injured leg. No significant effects were observed for static balance (all $P \geq 0.137$). Dynamic balance showed a group by time effect for the non-injured leg ($F_{3,117} = 4.1$, $P = 0.009$); dynamic balance improved significantly more over time in the standard care vs. cross-education group ($P \leq 0.012$). A time effect was found for both legs ($P < 0.001$). Dynamic balance of the reconstructed leg, relative to pre-surgery, showed 5% deficit 5 weeks post-surgery and 6% improvement 26 weeks post-surgery. Dynamic balance of the non-injured leg, relative to pre-surgery, improved 5% and 7% respectively 12 and 26 weeks post-surgery (all $P \leq 0.001$). The time effect of the non-injured leg’s single leg hop distance approaches significance ($F_{1,38} = 4.2$, $P = 0.050$).

### 6.4 Discussion

Twenty-six weeks of standard care improved self-reported knee function and neuromuscular function relative to pre-surgery but cross-education as an adjuvant to standard care did not further improve rehabilitation from ACL reconstruction.

#### 6.4.1 Primary outcome

Self-reported function did not differ between the cross-education and standard care groups, which is consistent with a previous orthopedic study [20] and supports the idea that the cross-education effect is too small to significantly improve activities of daily living [13]. However, there is also evidence to the contrary [21] but baseline differences and small (~8%) between-group differences after the intervention question the clinical relevance of those data. Our pre- and post-surgical scores on the HCK questionnaire were comparable to previous research [26] and reflect significant improvement (43%) in subjective knee function at 6 months post-surgery vs. pre-surgery in response to standard care without additional gains due to cross-education.
### Table 6.3 | Multi-joint neuromuscular functions of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Pre-surgery</th>
<th>post-surgery</th>
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<tr>
<td></td>
<td></td>
<td>5 weeks</td>
<td>12 weeks</td>
<td>26 weeks</td>
</tr>
<tr>
<td>ACL reconstructed leg (Nm/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-leg standing balance, eyes open (s)</td>
<td>Standard care</td>
<td>60 ± 0</td>
<td>60 ± 1</td>
<td>60 ± 0</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>60 ± 0</td>
<td>59 ± 4</td>
<td>60 ± 0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>60 ± 0</td>
<td>59 ± 4</td>
<td>60 ± 0</td>
</tr>
<tr>
<td>One-leg standing balance, eyes closed (s)</td>
<td>Standard care</td>
<td>28 ± 21</td>
<td>26 ± 19</td>
<td>31 ± 20</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>23 ± 18</td>
<td>29 ± 23</td>
<td>26 ± 22</td>
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<tr>
<td></td>
<td>Combined</td>
<td>26 ± 20</td>
<td>27 ± 21</td>
<td>28 ± 21</td>
</tr>
<tr>
<td>Star excursion balance test, composite score (% leg length)(^{a})</td>
<td>Standard care</td>
<td>79 ± 7</td>
<td>77 ± 9</td>
<td>83 ± 9</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>80 ± 8</td>
<td>75 ± 7</td>
<td>82 ± 7</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>80 ± 7</td>
<td>76 ± 8(\dagger)</td>
<td>83 ± 8</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>85 ± 10(\dagger)</td>
</tr>
<tr>
<td>Single leg hop test (cm)</td>
<td>Standard care</td>
<td>117 ± 37</td>
<td>——</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>121 ± 39</td>
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<tr>
<td></td>
<td>Combined</td>
<td>119 ± 37</td>
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### Table 6.3 | (Continued)

<table>
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<th>post-surgery</th>
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<tr>
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</tr>
<tr>
<td>Non-injured leg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-leg standing balance, eyes open (s)</td>
<td>Standard care</td>
<td>60 ± 0</td>
<td>60 ± 0</td>
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<tr>
<td></td>
<td>Standard care + XED</td>
<td>60 ± 0</td>
<td>60 ± 0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>60 ± 0</td>
<td>60 ± 0</td>
</tr>
<tr>
<td>One-leg standing balance, eyes closed (s)</td>
<td>Standard care</td>
<td>31 ± 21</td>
<td>30 ± 20</td>
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<tr>
<td></td>
<td>Standard care + XED</td>
<td>27 ± 24</td>
<td>31 ± 26</td>
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<tr>
<td></td>
<td>Combined</td>
<td>30 ± 22</td>
<td>30 ± 22</td>
</tr>
<tr>
<td>Star excursion balance test, composite score (% leg length)</td>
<td>Standard care</td>
<td>80 ± 9</td>
<td>83 ± 9*</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>83 ± 7</td>
<td>81 ± 9</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>81 ± 8</td>
<td>83 ± 9</td>
</tr>
<tr>
<td>Single leg hop test (cm)</td>
<td>Standard care</td>
<td>133 ± 32</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>147 ± 33</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>139 ± 33</td>
<td>——</td>
</tr>
</tbody>
</table>

XED, cross-education

* the composite score is expressed as the mean reaching distance, relative to leg length, of the the eight directions.

*, significant difference between groups (P < 0.05); †, different compared to pre-surgery (P < 0.05)
6.4.2 Maximal leg strength
This is the first study that examined the long-term effects of cross-education training in patients after ACL reconstruction. In healthy adults, the effects of cross-education on maximal voluntary muscle strength can last up to 12 weeks [37] and in patients up to 26 weeks after a wrist fracture [20]. Unlike in a previous study at eight weeks after ACL reconstruction, we found no cross-education effects at any point up to 26 weeks after surgery, making it also not possible to compare the time course of cross-education between patients and healthy adults. How and if at all in that study [15] it was cross-education that improved quadriceps function in the reconstructed leg in addition to standard care is unclear because, unlike previous cross-education studies [13,14], cross-education actually occurred in the absence of a training effect in the trained leg [15]. The extremely high levels of maximal quadriceps torque at baseline (~4.9 Nm/kg [15]) compared with the present (~3.4 Nm/kg) and other studies (~2.8 Nm [5,7,38]) make it additionally difficult to compare the training and cross-education data between studies. In total, it seems that the cross-education effects are small and unreliable under such clinical conditions.

The rate of change in MVC torques was similar for the quadriceps and hamstring muscles but showed a different pattern in the two legs. Quadriceps and hamstring MVCs of the reconstructed leg showed a ~40% deficit at 5 weeks post-surgery relative to pre-surgery but this deficit diminished and was ~18% at 12 weeks post-surgery and changed into 8% improvement at 26 weeks post-surgery. In contrast, the non-injured leg showed a monotonic 7-18% increase from pre-surgery to 26 weeks post-surgery. Only a handful of studies report the time course of MVC torques after ACL surgery [4,39,40], so our data help understand the longitudinal strength development of the reconstructed and non-injured leg. After 26 weeks of standard care, isometric quadriceps MVCs of the reconstructed leg were 6% above pre-surgery levels and were higher than 3.0 Nm/kg, a value linked to good patient-reported outcomes [41,42].

6.4.3 Voluntary quadriceps activation
In addition to standard care, cross-education improved the reconstructed leg’s CAR, suggesting that cross-education can reduce activation failure, a possible cause of quadriceps weakness [8]. However, the effect of cross-education on the CAR was only observed five weeks post-surgery, which makes it of small clinical relevance. At five and 12 weeks post-surgery, the twitch interpolation technique provided evidence that the voluntary drive to the quadriceps muscles was reduced and the size of the potentiated twitch force indicated quadriceps muscle weakness. These
activation deficits were only observed in the reconstructed leg.

The CAR and not the twitch interpolation technique has been widely used in ACL studies [5,41,43]. A systematic review showed that the CAR is on average 84% and 89% for the reconstructed and non-injured leg respectively [43]. The CAR of our ACL patients at 26 weeks post-surgery was higher and even above the 95%-threshold, a marker of healthy quadriceps function [43].

6.4.4 Force control
Our data support the idea that resistance training can improve force control of the quadriceps [28]. Force accuracy and variability but not knee joint position sense improved in the reconstructed and non-injured leg by 12 (17-56%) and 26 (22-34%) weeks post-surgery relative to pre-surgery. Also, force control at week 12 is already better than reported in healthy controls [7]. Previous studies reported impaired force accuracy [44] and variability [45] in the reconstructed leg 16-18 months post-surgery. Inadequate force control increases knee joint loadings, which, over time, could initiate or accelerate knee osteoarthritis [46]. Future research should investigate if ACL reconstructed patients with good force control are indeed less vulnerable to develop knee osteoarthritis.

6.4.5 Multi-joint neuromuscular function
Rehabilitation did not improve static balance but dynamic balance, measured by the SEBT, showed an improvement of ~7% after 26 weeks of standard care relative to pre-surgery. However, both legs still showed a ~6% (0.42 SDs) deficit at 26 weeks post-surgery relative to healthy controls [7], confirming previous findings [47]. Also, both legs had a SEBT composite score of below 94% leg length, which means that our ACL patients were at increased risk to sustain a lower extremity injury [48]. Rehabilitation programs should focus on improving dynamic balance before ACL reconstructed patients return to full sport participation.

The hop distance, measured before and 26 weeks after surgery, did not differ between groups or over time and was comparable to previous research [4]. The hop test simulates loads encountered during sport-specific movements [49] where a limb symmetry of >90% is a criterion for return to sports [50]. Not surprisingly, our ACL patients, at 26 weeks post-surgery, were not yet ready to return to sports with a limb symmetry of 85%. However, it might be better to use the hop performance of healthy controls as a reference for return to sports because bilateral reductions in hop distance were observed up to 24 month after ACL reconstruction [4].
6.4.6 Study limitations
After randomization there were seven more patients in the standard care (n = 25) compared with the cross-education group that had three fewer patients than required by sample size estimation. However, post mortem analyses of adding three more non-existing patients to the cross-education group revealed that the sample size was not the problem but that the between-group differences were just too small.

The random group allocation resulted in a skewed sex distribution between groups by nine more females in the standard care vs. cross-education group. Compared to males, females have reported worse knee function after ACL reconstruction [51], were less likely to return to pre-injury sports level [52,53], and were at increased risk to sustain a second ACL injury [53,54] especially to the contralateral leg [54,55]. The cause of these sex differences is unclear [56,57] but might have biased the results of the standard care group.

6.4.7 Conclusions
As routinely reported, standard rehabilitation programs, specifically targeting the reconstructed leg, recover self-reported knee function and neuromuscular function after surgery. Twenty-six weeks of standard care improved self-reported knee function and neuromuscular function relative to pre-surgery, but cross-education, as an adjuvant to standard care, did not further accelerate rehabilitation from ACL reconstruction. Under such clinical conditions, the cross-education effects are too small and unreliable across studies. Cross-education training could still serve as an adjuvant to standard rehabilitation of patients with orthopedic injuries in which training the injured limb is not possible due to immobilization.

Acknowledgements and conflicts of interest
This work was supported by start-up fund 653013 from the University Medical Center Groningen. The authors thank BSc. A. Doornbos, BSc. A. Elsinghorst, BSc, BSc. K. Koorenhof, and BSc. L. Winkelhorst for their assistance with the data collection, MSc. E. Nieman and MSc. I. Brookman for performing the pilot study, Dr. R. Stewart for his assistance with the statistical analysis, and Medisch Centrum Zuid-Flytta for providing the research facilities.

The authors report no conflicts of interest of any kind that are associated with the current study.

References


Cross-education after ACL reconstruction


[51] Ageberg E, Forssblad M, Herbertsson P, Roos EM. Sex differences in patient-reported


**Appendices**

**Appendix 6.1 | Rehabilitation program after ACL reconstruction**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Week</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1: Active mobilization</td>
<td>1-4</td>
<td>- Mobilization, focus on passive extension (first 2 weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Reducing inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Quadriceps strength 3x15 reps per leg (leg press, leg extension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Straight leg raises 3x10 reps per leg</td>
</tr>
<tr>
<td>Phase 2: Basic strength</td>
<td>4-12</td>
<td>- Minimizing inflammation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Quadriceps strength 3x15 reps per leg (leg press, leg extension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Hamstring strength 3x15 reps per leg (leg curl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Squats 3x15 reps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Good mornings 3x15 reps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Straight leg raises 3x10 reps per leg</td>
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<tr>
<td></td>
<td></td>
<td>- Step ups 3x10 reps per leg</td>
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<tr>
<td></td>
<td></td>
<td>- Balance and core stability exercises</td>
</tr>
<tr>
<td>Phase 3: Maximal strength</td>
<td>12-24</td>
<td>- Strength exercises as above (4x10 reps or pyramid strength 14/12/10/8 reps, progression after a few weeks to 10/8/6/4 reps)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Balance and core stability exercises</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Start running, with minimal change in direction/pivoting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Basic 2 legged jumping tasks</td>
</tr>
<tr>
<td>Phase 4: Power and jumping</td>
<td>24-36</td>
<td>- Power training, working on strength deficits</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Progress running, directional changes/pivoting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Progress from 2 legged to 1 legged jumping tasks</td>
</tr>
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### Appendix 6.2 | Maximal hamstring torque of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Pre-surgery</th>
<th>post-surgery</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td>12 weeks</td>
</tr>
<tr>
<td><strong>ACL reconstructed leg (Nm/kg)</strong></td>
<td>Standard care</td>
<td>1.9 ± 0.6</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>2.2 ± 0.5</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>2.0 ± 0.6</td>
<td>——</td>
</tr>
<tr>
<td>Eccentric 60°/s</td>
<td>Standard care</td>
<td>1.3 ± 0.4</td>
<td>0.9 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.5 ± 0.3</td>
<td>0.8 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.4 ± 0.4</td>
<td>0.8 ± 0.3†</td>
</tr>
<tr>
<td>Isometric</td>
<td>Standard care</td>
<td>1.2 ± 0.4</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.2 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.2 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td>Concentric 60°/s</td>
<td>Standard care</td>
<td>1.1 ± 0.4</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.2 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.1 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td>Concentric 120°/s</td>
<td>Standard care</td>
<td>1.0 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Concentric 180°/s</td>
<td>Standard care</td>
<td>1.0 ± 0.3</td>
<td>——</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>1.1 ± 0.3</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.1 ± 0.3</td>
<td>1.0 ± 0.4</td>
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## Cross-education after ACL reconstruction

<table>
<thead>
<tr>
<th>Variables</th>
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<tr>
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<td>12 weeks</td>
</tr>
<tr>
<td>Non-injured leg (Nm/kg)</td>
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<td></td>
<td></td>
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<tr>
<td>Eccentric 60°/s</td>
<td>Standard care</td>
<td>2.2 ± 0.6</td>
<td>2.4 ± 0.7</td>
</tr>
<tr>
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<td>Standard care + XED</td>
<td>2.6 ± 0.5</td>
<td>2.5 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>2.4 ± 0.6</td>
<td>2.4 ± 0.6</td>
</tr>
<tr>
<td>Isometric</td>
<td>Standard care</td>
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<td>1.5 ± 0.4</td>
</tr>
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<td>Standard care + XED</td>
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<td>Combined</td>
<td>1.5 ± 0.4</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>Concentric 60°/s</td>
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<td>1.3 ± 0.4</td>
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<td>Standard care + XED</td>
<td>1.3 ± 0.3</td>
<td>1.4 ± 0.3</td>
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<td>Combined</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Concentric 120°/s</td>
<td>Standard care</td>
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<td>1.1 ± 0.5</td>
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<tr>
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<td>Standard care + XED</td>
<td>1.2 ± 0.3</td>
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<td></td>
<td>Combined</td>
<td>1.1 ± 0.3</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Concentric 180°/s</td>
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<td>Standard care + XED</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.4</td>
</tr>
</tbody>
</table>

XED, cross-education; †, different compared to pre-surgery (P < 0.05)
### Appendix 6.3 | Quadriceps voluntary force and muscle activation of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Pre-surgery</th>
<th>post-surgery</th>
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</thead>
<tbody>
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<td>12 weeks</td>
</tr>
<tr>
<td><strong>ACL reconstructed leg</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potentiated doublet force (Nm)</td>
<td>Standard care</td>
<td>69.9 ± 19.4</td>
<td>54.8 ± 18.5</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>82.6 ± 31.3</td>
<td>61.1 ± 22.5</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>75.8 ± 26.1</td>
<td>57.4 ± 20.0†</td>
</tr>
<tr>
<td>Isometric MVC (Nm)</td>
<td>Standard care</td>
<td>173.5 ± 61.6</td>
<td>95.3 ± 66.2</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>218.3 ± 89.9</td>
<td>133.5 ± 61.3</td>
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<tr>
<td></td>
<td>Combined</td>
<td>194.5 ± 78.3</td>
<td>110.9 ± 65.8†</td>
</tr>
<tr>
<td>Estimated MVC (Nm)</td>
<td>Standard care</td>
<td>133.4 ± 41.9</td>
<td>82.0 ± 43.9</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>162.8 ± 67.5</td>
<td>110.4 ± 50.6</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>147.2 ± 56.4</td>
<td>93.6 ± 48.0†</td>
</tr>
<tr>
<td>Activation ratio (% of potentiated twitch)</td>
<td>Standard care</td>
<td>-25.6 ± 10.3</td>
<td>-7.3 ± 18.8</td>
</tr>
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<td>Standard care + XED</td>
<td>-28.8 ± 7.6</td>
<td>-16.8 ± 6.6</td>
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<tr>
<td></td>
<td>Combined</td>
<td>-27.1 ± 9.1</td>
<td>-11.1 ± 15.6†</td>
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</table>
## Appendix 6.3 | (Continued)

<table>
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<tr>
<th>Variables</th>
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<th>post-surgery</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>5 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Non-injured leg</td>
<td>Standard care</td>
<td>76.0 ± 20.8</td>
<td>74.0 ± 18.6</td>
</tr>
<tr>
<td>Potentiated doublet force (Nm)</td>
<td>Standard care + XED</td>
<td>93.7 ± 26.6</td>
<td>94.2 ± 30.9</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>84.3 ± 24.9</td>
<td>83.2 ± 26.6</td>
</tr>
<tr>
<td>Isometric MVC (Nm)</td>
<td>Standard care</td>
<td>190.3 ± 56.7</td>
<td>182.9 ± 56.6</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>233.2 ± 73.2</td>
<td>227.5 ± 80.0</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>210.4 ± 67.5</td>
<td>203.2 ± 70.8</td>
</tr>
<tr>
<td>Estimated MVC (Nm)</td>
<td>Standard care</td>
<td>149.5 ± 38.7</td>
<td>139.2 ± 37.8</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>181.5 ± 61.2</td>
<td>174.4 ± 63.4</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>164.5 ± 52.2</td>
<td>155.2 ± 53.3</td>
</tr>
<tr>
<td>Activation ratio (% of potentiated twitch)</td>
<td>Standard care</td>
<td>-23.9 ± 13.2</td>
<td>-27.8 ± 10.5</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>-24.1 ± 6.8</td>
<td>-27.0 ± 12.9</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>-24.0 ± 10.5</td>
<td>-27.4 ± 11.5</td>
</tr>
</tbody>
</table>

XED, cross-education; †, different compared to pre-surgery (P < 0.05)
### Appendix 6.4 | Quadriceps force control of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
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<th>post-surgery</th>
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<td>12 weeks</td>
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</tbody>
</table>

#### Force accuracy ACL reconstructed leg (Nm)

| Eccentric | Standard care | 13.1 ± 5.9 | 11.7 ± 5.9 | 8.4 ± 3.3 | 8.9 ± 6.0 |
|           | Standard care + XED | 13.5 ± 9.2 | 11.7 ± 4.8 | 10.5 ± 6.3 | 9.5 ± 5.4 |
|           | Combined | 13.3 ± 7.2 | 11.7 ± 5.4 | 9.3 ± 4.8† | 9.1 ± 5.7† |

| Isometric | Standard care | 3.0 ± 4.4 | 1.0 ± 1.1 | 1.1 ± 0.6 | 1.7 ± 1.6 |
|           | Standard care + XED | 1.7 ± 0.8 | 1.3 ± 1.2 | 1.1 ± 0.5 | 1.6 ± 1.0 |
|           | Combined | 2.5 ± 3.5 | 1.1 ± 1.1† | 1.1 ± 0.6† | 1.6 ± 1.4 |

| Concentric | Standard care | 14.0 ± 14.0 | 7.0 ± 4.2 | 7.5 ± 5.0 | 8.3 ± 8.4 |
|           | Standard care + XED | 6.9 ± 3.5 | 6.9 ± 3.4 | 6.5 ± 4.7 | 6.2 ± 6.3 |
|           | Combined | 11.3 ± 11.7 | 6.9 ± 3.8 | 7.1 ± 4.8 | 7.5 ± 7.6† |

#### Force variability ACL reconstructed leg (% of mean force)

| Eccentric | Standard care | 25.5 ± 18.0 | 30.2 ± 19.3 | 22.3 ± 11.8 | 16.5 ± 7.7 |
|           | Standard care + XED | 22.0 ± 12.9 | 31.6 ± 15.9 | 23.0 ± 19.1 | 18.8 ± 8.4 |
|           | Combined | 24.2 ± 16.1 | 30.8 ± 17.7† | 22.6 ± 15.1 | 17.4 ± 8.0† |

| Isometric | Standard care | 3.2 ± 1.2 | 2.8 ± 0.9 | 2.6 ± 1.1 | 2.4 ± 0.6 |
|           | Standard care + XED | 2.9 ± 1.1 | 3.1 ± 1.2 | 2.5 ± 0.8 | 2.3 ± 0.8 |
|           | Combined | 3.1 ± 1.1 | 3.0 ± 1.0 | 2.5 ± 1.0† | 2.3 ± 0.7† |

| Concentric | Standard care | 17.6 ± 7.3 | 14.0 ± 8.5 | 14.0 ± 9.0 | 12.8 ± 5.0 |
|           | Standard care + XED | 15.7 ± 8.5 | 14.5 ± 7.4 | 12.3 ± 5.5 | 12.5 ± 7.3 |
|           | Combined | 16.8 ± 7.7 | 14.2 ± 8.0 | 13.2 ± 7.6† | 12.7 ± 5.8† |
### Cross-education after ACL reconstruction

**Variables** Group | Pre-surgery | post-surgery
--- | --- | --- | ---

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>5 weeks</th>
<th>12 weeks</th>
<th>26 weeks</th>
</tr>
</thead>
</table>

#### Force accuracy non-injured leg (Nm)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Standard care + XED</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
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<td>12.5 ± 5.0</td>
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<tr>
<td></td>
<td>10.4 ± 4.7</td>
<td>10.7 ± 5.7</td>
<td>10.5 ± 5.1(^\dagger)</td>
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<tr>
<td></td>
<td>8.3 ± 4.8</td>
<td>7.8 ± 3.7</td>
<td>8.1 ± 4.3(^\dagger)</td>
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<td>7.8 ± 4.8</td>
<td>8.7 ± 5.6</td>
<td>8.2 ± 5.1(^\dagger)</td>
</tr>
<tr>
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<td>1.7 ± 0.5</td>
<td>2.6 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>2.8 ± 3.9</td>
<td>2.8 ± 4.4</td>
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<tr>
<td></td>
<td>1.8 ± 0.9</td>
<td>1.5 ± 0.6</td>
<td>1.7 ± 0.8</td>
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<tr>
<td></td>
<td>1.7 ± 0.9</td>
<td>1.9 ± 1.0</td>
<td>1.8 ± 0.9</td>
</tr>
<tr>
<td>Concentric</td>
<td>14.3 ± 11.3</td>
<td>7.6 ± 3.5</td>
<td>11.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>11.4 ± 9.8</td>
<td>7.5 ± 4.4</td>
<td>9.8 ± 8.1</td>
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<tr>
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<td>10.0 ± 10.4</td>
<td>5.5 ± 3.5</td>
<td>8.0 ± 8.3(^\dagger)</td>
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<tr>
<td></td>
<td>10.8 ± 11.4</td>
<td>6.9 ± 5.3</td>
<td>9.2 ± 9.6(^\dagger)</td>
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</table>

#### Force variability non-injured leg (% of mean force)\(^b\)

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<tr>
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<td>20.0 ± 12.7</td>
<td>17.0 ± 10.6</td>
<td>18.8 ± 11.9(^\dagger)</td>
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<td>18.8 ± 9.3</td>
<td>15.0 ± 4.9</td>
<td>17.1 ± 7.8(^\dagger)</td>
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<td>15.3 ± 5.9</td>
<td>16.4 ± 6.1</td>
<td>15.8 ± 5.9(^\dagger)</td>
</tr>
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<td>3.1 ± 1.1</td>
<td>3.0 ± 1.0</td>
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<td>3.0 ± 1.4</td>
<td>2.8 ± 0.9</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
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<td>2.2 ± 0.8</td>
<td>2.7 ± 0.8</td>
<td>2.5 ± 0.8(^\dagger)</td>
</tr>
<tr>
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<td>3.3 ± 3.4</td>
<td>2.5 ± 0.7</td>
<td>2.8 ± 2.2</td>
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<tr>
<td>Concentric</td>
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<td>18.7 ± 9.8</td>
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<tr>
<td></td>
<td>14.6 ± 5.9</td>
<td>16.5 ± 8.9</td>
<td>15.4 ± 7.3</td>
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<td>12.8 ± 8.5</td>
<td>10.0 ± 3.4</td>
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<td>13.3 ± 6.4</td>
<td>11.0 ± 5.5</td>
<td>12.4 ± 6.1(^\dagger)</td>
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</tbody>
</table>

\(^a\) force accuracy is expressed as the absolute difference between the produced force and the target force.

\(^b\) force variability was quantified by the SD of the produced force divided by the mean force (i.e., coefficient of variation).

\(\text{XED, cross-education; } \dagger, \text{ different compared to pre-surgery (P < 0.05).}\)
### Appendix 6.5 | Knee joint proprioception of the ACL reconstructed and non-injured leg (mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group</th>
<th>Pre-surgery</th>
<th>post-surgery</th>
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<tbody>
<tr>
<td></td>
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<td>5 weeks</td>
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<tr>
<td><strong>Proprioception ACL reconstructed leg (°)</strong></td>
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<td></td>
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<tr>
<td>15°</td>
<td>Standard care</td>
<td>3 ± 3</td>
<td>3 ± 2</td>
</tr>
<tr>
<td></td>
<td>Standard care + XED</td>
<td>3 ± 3</td>
<td>3 ± 2</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>3 ± 3</td>
<td>3 ± 2</td>
</tr>
<tr>
<td>30°</td>
<td>Standard care</td>
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</tr>
<tr>
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<td>2 ± 2</td>
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<td>3 ± 2</td>
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<tr>
<td><strong>Proprioception non-injured leg (°)</strong></td>
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<td>Combined</td>
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<td>3 ± 2</td>
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<td>Post-surgery</td>
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<td>-------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
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<td>12 weeks</td>
<td>26 weeks</td>
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<tr>
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<td>3 ± 2</td>
<td>4 ± 3</td>
</tr>
</tbody>
</table>

Variables: 45°, 60°

*proprioception is expressed as the absolute error relative to the target position
XED, cross-education; †, different compared to pre-surgery (P < 0.05)