Expansory Muscle Strength Training in patients After Total Laryngectomy; A Feasibility Pilot Study


DOI
10.1177/0003489420931889

Publication date
2020

Document Version
Final published version

Published in
The Annals of Otology Rhinology & Laryngology

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/in-the-netherlands/you-share-we-take-care)

Link to publication

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)
Expiratory Muscle Strength Training in patients After Total Laryngectomy: A Feasibility Pilot Study

Klaske E. van Sluis, MSc1,2*, Anne F. Kornman, MSc1*, Wim G. Groen, PhD3, Michiel W. M. van den Brekel, MD, PhD1,2,4, Lisette van der Molen, PhD1,5, Bari Hoffman-Ruddy, PhD5, and Martijn M. Stuiver, PhD1,6,7

Abstract
Objectives: Expiratory muscle strength training (EMST) is a threshold based device-driven treatment for improving expiratory pressure. EMST proved to be effective in different patient groups to improve cough function. To date, EMST has not been tested in the total laryngectomy population (TL).

Methods: This prospective, randomized case-series study examined feasibility, safety, and compliance of EMST in a group of TL participants and its effects on pulmonary function, physical exertion, fatigue, and vocal functioning. Ten TL participants were included in the study to perform a 4 till 8 weeks of EMST. Objective and subjective outcome measures included manometry, spirometry, cardio pulmonary exercise testing (CPET), voice recordings, and patient reported outcome measures. Group means were reported and estimates of the effect are shown with a 95% confidence interval, using single sample t-tests.

Results: Nine participants completed the full study protocol. Compliance to the training program was high. All were able to perform the training, although it requires adjustments of the device and skills of the participants. Maximum expiratory pressure (MEP) and vocal functioning in loudness improved over time. After EMST no changes were seen in other objective and subjective outcomes.

Conclusions: EMST appears to be feasible and safe after total laryngectomy. MEP improved over time but no improvement in the clinically relevant outcome measures were seen in this sample of relatively fit participants. Further investigation of the training in a larger group of participants who report specifically pulmonary complaints is recommended to investigate if the increase in MEP results in clinical benefits.

Level of Evidence: 4

Keywords
head and neck cancer, total Laryngectomy, cough, bronchoesophagology, voice, clinical outcomes research

Introduction

Total laryngectomy (TL), which involves surgical removal of the larynx, leads to lifelong changes in voice, swallowing and airway. Pulmonary driven speech can be re-established with insertion of a voice prosthesis, also called tracheoesophageal speech.1 Compared to healthy individuals the voices of tracheoesophageal speakers have a rough voice quality, reduced loudness, and limited range.2

After TL pulmonary condition is affected as air entering the lungs via the stoma is not warmed and humidified by the nose and upper respiratory tract, which leads to impaired mucociliary clearance. Impaired mucociliary function is the main cause of pulmonary complaints such as increased mucus production and forced mucus expectoration after TL.3-5 Warming and humidifying the inhaled air is a key factor in improving pulmonary condition. Over the years several options were developed: external humidifiers, stoma cloths (eg, bibs), and heat-moisture-exchange devices (HME-devices).5-8 Both stoma cloths and HME-devices are proved to be effective in everyday life and can reduce pulmonary problems in this patient group.5-11 Nevertheless, pulmonary complaints including increased mucus production and forced mucus expectoration are still present after TL.12,13

The altered anatomy results in a physiological altered cough function after TL. Removal of the larynx eliminates the ability to generate subglottic pressure prior to cough onset. Cough requires high expiratory airflow to aerosolize and remove material that is unable to be removed by
mucociliary action. Cough “strength” is determined by the ability to generate high expiratory pressures immediately prior to cough onset and by the volume of air that is expelled from the airways. With the absence of the ability to build up subglottic pressure, it is assumed that after a TL increased cough strength can only be achieved by increasing the volume and speed of cough expiratory airflow. To date, cough function after TL and the potential benefit of rehabilitation techniques have not been studied.

A well-known rehabilitation technique to improve cough function is expiratory muscle strength training (EMST). Recently, the use of EMST has been evaluated in several studies, including different patient groups such as Parkinson’s disease, sleep apnea, head and neck cancer patients with dysphagia, stroke, amyotrophic lateral sclerosis, supraccricoid partial laryngectomy, and healthy participants. In several populations, to date, EMST has been shown to increase expiratory pressure generation by 30% to 150%, with an average increase of approximately 50% in a 4-week period of time. Most of the clinical studies cited above aimed at improving cough strength to improve clearing of aspiration of oral intake or saliva. EMST has not been tested in the TL population.

The main objective of the present study is to evaluate feasibility, safety, and compliance of EMST in individuals who have undergone TL. Subsequently, objective and subjective outcomes of the effects of EMST on pulmonary function, physical exertion, fatigue, and vocal functioning are assessed.

Materials and Methods

This prospective, randomized case-series study examined feasibility of EMST and its effects on pulmonary function and voice, in a group of male TL participants, who were at least a half year post surgery and, if applicable, post-operative (chemo) radiation. Participants were screened and recruited from the head and neck department of the Netherlands Cancer Institute-Antoni van Leeuwenhoek, Amsterdam, The Netherlands. Exclusion criteria were: recurrence of head and neck cancer, a history of lung cancer, severe asthma, tuberculosis, uncontrolled or untreated hypertension, a heart attack in the last year, or abdominal hernia. The study was approved by the medical ethical review committee of the Netherlands Cancer Institute (registration nr. NL60167.031.16.).

**Expiratory Muscle Strength Training and Adjustment to Use After TL**

EMST150 (Aspire Products) is a threshold based device-driven treatment for improving expiratory pressure generating capacity. EMST employs a handheld training device consisting of a plexiglass tube. Inside the device is a variable tension spring controlling a valve that is calibrated in pressure, adjustable from 30 till 150 cmH2O. When enough pressure is developed, the valve opens, allowing air to flow through the trainer. The patient is instructed to exhale forcefully through the device. In this way, EMST targets the rectus abdominis and internal intercostal muscles through a program of progressive overloading which is an exercise stimulus specific for forcible expiration.

To adjust the use of the EMST150 device for TL participants, we developed and produced an adaptor to connect the device at the adhesive baseplate in front of the tracheostoma. This adaptor contains an opening on top to allow inhalation which can be occluded manually, a small lumen for use of the voice prosthesis plug, and a tube which enables connection with a manometer (Figures 1 and 2).

**EMST Study Training Protocol**

All participants performed 4 weeks of EMST (period A) which consisted of five sets of five repetitions across 5 days per week. Strength measurements and subsequent adjustment of the pressure of the EMST device were performed at baseline and after each training week. Participants were instructed to perform their training sessions at home and log each training with details in a diary to check compliance. During the
Feasibility, Safety, and Compliance

The main objective of the study was to evaluate feasibility, safety, and compliance with the EMST program. Any difficulties regarding participants’ performance of the training and assessment procedures were documented. Participants were instructed to log every training session and reflect on their experiences in a diary. At the end of the training program participants filled in a short questionnaire on whether they found the training feasible and whether they could stay motivated during the period of training.

Objective and Subjective Outcome Measures

The effects of EMST on pulmonary function, physical exertion, fatigue, and vocal functioning are assessed with manometry, spirometry, cardio pulmonary exercise testing (CPET), voice recordings, and questionnaires. Time points of the assessments are shown in Table 1. MEP in cmH2O was obtained with a calibrated digital manometer (Druck DPI 705) connected to the adapter whilst the EMST device was adjusted to the maximum pressure of 150 cmH2O and connected to the tracheostoma. Participants were instructed to sit, take a deep breath, occlude the adapter, and exhale as forcefully as possible. Peak Expiratory Flow (PEF) in L/min was obtained with a Micro 1 spirometer combined with a Microgard II filter (PT Medical) which was placed directly on the baseplate of the stoma. Participants were instructed to inhale calm but deep and then exhale as forcefully and fast as they could. A series of three forced expirations was used to obtain MEP and PEF, the mean of the three trials was used for the analysis. With a calibrated ergospirometry system (Jaeger Masterscreen CPX, Houten, The Netherlands), connected to the stoma, vital capacity (VC), and forced expiratory volume in the first second (FEV1) were measured. Participants performed a Cardio Pulmonary Exercise Test (CPET) on an electronically braked cycle ergometer (Lode Corival, ProCare, Groningen, The Netherlands). An adapter was made to fit the flow turbine directly to the baseplate in front of the tracheostoma and a headband for fixation was used to support the adapter and flow turbine. The ventilatory efficiency was defined by minute volume of expired air relative to volume of CO2 produced (VE/VCO2). Patients cycled till they had reached a respiratory exchange ratio of 1.0 thus precluding them from a maximal exertion. Directly after finishing the test, participants were asked to rate their perceived level of exertion and dyspnea on a Borg scale.28,29 Voice recordings were made with a head mounted microphone and recorded with Audacity software.30 Participants were instructed to perform a sustained vowel /a/ as long as possible to measure maximum phonation time (MPT). Vocal range in Herz (Hz) and dynamic range in deciBel (dB) were measured as an outcome of the difference between the lowest and highest and softest and loudest /a/ produced,
respectively. The best of three attempts was used for each value. All voice recordings were acoustically analyzed with PRAAT software. Self-reported vocal functioning is assessed with the Voice Handicap Index-10 (VHI-10), self-reported fatigue with the Short Fatigue Questionnaire (SFQ), and self-reported pulmonary functioning with the clinical COPD questionnaire (CCQ).

Statistical Analysis

Due to lack of preliminary data with regard to pulmonary exercise programs in TL patients, there was no meaningful way to perform sample size calculations related to the quantitative outcome. All data was analyzed using SPSS software. Accordingly, no significance tests were performed. Group means were estimated with a 95% confidence interval, using single sample t-tests.

Results

Ten participants were included and signed informed consent. Participants age ranged from 50 to 73 years, and all were tracheo-esophageal speakers (characteristics are presented in Table 2).

Feasibility, Compliance, and Safety

Using the EMST device with help of an adapter on the tracheostoma of the TL participants appeared to be generally feasible. All participants could perform the training. One participant withdrew from the study after 1 week due to unrelated medical reasons. For the remaining nine participants, compliance to the allocated training program was 95.5%. According to the final short questionnaire, participants did not experience problems to stay motivated during the training weeks. Minor problems included leakage of air underneath the adhesive, which was reported by four of the participants. Two participants occasionally experienced dizziness during and shortly after the training. Three participants were not able to plug the voice prosthesis prior to the training, and continued training without plug. From the six participants who did plug their voice prosthesis before training, three mentioned that plugging was a hassle.

Regarding to safety, one adverse event occurred with one of the participants in his fourth EMST training week. After a training session with the EMST, the voice prosthesis was not in situ anymore. A new voice prosthesis was placed and an X-thorax was made which showed that the voice prosthesis was not in the lungs. All participants and the medical ethical review committee were informed.

Objective and Subjective Outcome Measures

Results on pulmonary function, physical exertion, fatigue, and vocal functioning are presented in Table 3. We observed a non-linear increase in the manometry outcome MEP. During the first four training weeks mean MEP increased from 125.5 cmH2O to 174.8 cmH2O during the first 4 weeks (95% CI: baseline 110.4-140.6, 4 week 152.8-196.8). After 4 weeks, MEP stabilized, with no evidence for differences in detraining between group 1 and group 2 (Figure 3). Overall, MEP decreased slightly to a mean of 164.9 cmH2O (95% CI: 141.8-189.0) at the end of the follow-up. Three of the nine participants achieved a MEP-score above 187.5 cmH2O during the first four training weeks. For those participants, training at 80% of the mean MEP was not possible from that moment onward, since the maximum setting of the EMST is 150 cmH2O. These participants continued their training on the maximum setting of the EMST150-device. The three participants who used no plug during training showed increase of the MEP as well.
We observed no effect on spirometry outcome PEF over time (Figure 4). Mean PEF values were 455.9 L/min at baseline and 445.5 L/min after 4 weeks (95% CI: baseline 374.8-537.0, 4 week 356.0-535.0). In this sample, no effect of detraining was seen in PEF after reducing or stopping the training with a mean PEF value of 405.3 at week 8 (95% CI: 318.8-492.0).

No changes over time were found for self-reported pulmonary problems (CCQ), vocal functioning (VHI-10), fatigue (SFQ). No differences were found for outcomes in physical exertion (CPET, Borg scales). Objective assessment of vocal functioning showed no differences in MPT and vocal range in Hz. Exception was dynamic range in dB, which increased from 26.4 dB (95% CI: 21.7-31.0) to 31.9 dB (95% CI: 28.8-35.0) after 4 weeks of training. After period B vocal range in dB returned back to baseline values (mean 27.6 dB 95% CI: 23.1-32.2).

**Discussion**

To date, this is the first study to investigate feasibility, safety, and compliance of EMST in a group of TL participants.

---

**Table 2. Participant Characteristics.**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age in Years</th>
<th>Time since TL in Years</th>
<th>Timing Radiotherapy</th>
<th>Flap Reconstruction</th>
<th>Neck Dissection</th>
<th>Tracheo Esophageal Speech: Manually/Hands Free Device</th>
<th>Randomization Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>13</td>
<td>Post-surgery</td>
<td>No</td>
<td>Both sides</td>
<td>Freehands</td>
<td>Stop Training</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>18</td>
<td>Pre-surgery</td>
<td>Unknown†</td>
<td>Unknown†</td>
<td>Manually</td>
<td>Continue Training</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>3</td>
<td>Pre-surgery</td>
<td>No</td>
<td>Both sides</td>
<td>Both, alternating</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>68</td>
<td>1</td>
<td>Pre-surgery</td>
<td>PM-flap</td>
<td>No</td>
<td>Manually</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>15</td>
<td>Pre-surgery</td>
<td>No</td>
<td>Both sides</td>
<td>Freehands</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>7</td>
<td>Pre-surgery</td>
<td>No</td>
<td>No</td>
<td>Manually</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>3</td>
<td>Pre-surgery</td>
<td>No</td>
<td>Both sides</td>
<td>Both, alternating</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>10</td>
<td>Post-surgery</td>
<td>No</td>
<td>Both sides</td>
<td>Freehands</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>78</td>
<td>3</td>
<td>Post-surgery</td>
<td>No</td>
<td>Left side</td>
<td>Manually</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>20</td>
<td>Pre-surgery</td>
<td>Unknown†</td>
<td>Unknown†</td>
<td>Manually</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PM-flap, Pectoralis Major flap; TL, total laryngectomy.†No surgical information was available.

**Table 3. Mean, Standard Deviation, and Confidence Interval for the Outcome Measures of the Total Group of Participants at Baseline, Week 4 and Week 8.**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Wk 4</th>
<th>Wk 8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>MEP—cmH₂O</td>
<td>125.5 (19.6)</td>
<td>110.4-140.6</td>
<td>174.8 (28.6)</td>
</tr>
<tr>
<td>PEF—L/min</td>
<td>455.9 (116.4)</td>
<td>374.8-537.0</td>
<td>445.5 (116.4)</td>
</tr>
<tr>
<td>CPET—VE/VCO₂</td>
<td>29.5 (4.7)</td>
<td>25.9-33.1</td>
<td>28.4 (2.8)</td>
</tr>
<tr>
<td>Borg exertion scale</td>
<td>13.0 (1.7)</td>
<td>11.7-14.3</td>
<td>12.4 (1.3)</td>
</tr>
<tr>
<td>Borg dyspnea scale</td>
<td>2.7 (2.2)</td>
<td>1.0-4.4</td>
<td>2.2 (1.9)</td>
</tr>
<tr>
<td>FEV1—L</td>
<td>3.2 (0.7)</td>
<td>2.6-3.7</td>
<td>3.0 (0.6)</td>
</tr>
<tr>
<td>VC—L</td>
<td>4.3 (1.0)</td>
<td>3.5-5.1</td>
<td>4.1 (0.8)</td>
</tr>
<tr>
<td>Vocal range—Hz</td>
<td>144.6 (98.9)</td>
<td>62.0-227.3</td>
<td>147.0 (63.0)</td>
</tr>
<tr>
<td>Vocal range—dB</td>
<td>26.4 (5.6)</td>
<td>21.7-31.0</td>
<td>31.9 (3.7)</td>
</tr>
<tr>
<td>MPT—sec</td>
<td>12.5 (7.9)</td>
<td>5.9-19.0</td>
<td>12.2 (8.5)</td>
</tr>
<tr>
<td>VHI-10²</td>
<td>15.6 (10.0)</td>
<td>7.3-24.0</td>
<td>16.0 (9.7)</td>
</tr>
<tr>
<td>SFQ³³</td>
<td>8.1 (5.1)</td>
<td>4.2-12.0</td>
<td>8.44 (4.2)</td>
</tr>
<tr>
<td>CCQ total score³⁴</td>
<td>1.2 (0.8)</td>
<td>0.6-1.8</td>
<td>1.3 (0.7)</td>
</tr>
</tbody>
</table>

Abbreviations: CCQ, Clinical COPD Questionnaire; CPET, Cardio Pulmonary Exercise Testing; FEV1, forced expiratory volume in the first second; MEP, Maximum Expiratory Pressure; MPT, Maximum Phonation Time; PEF, Peak Expiratory Flow; SFQ, Short Fatigue Questionnaire; VC, Vital capacity; VHI-10, Voice Handicap Index 10 item version.
EMST appears to be somewhat challenging, but feasible. MEP improved over time but this did not seem clinically relevant for this group of relatively fit participants.

Challenges encountered the need for an adapter, skills of the participants with plugging the voice prosthesis, placing the EMST150 with an adaptor on the tracheostoma, and creating an airtight seal. One safety issue occurred with a participant presenting without a voice prosthesis after a training session. Nevertheless, compliance to the training program was high (>95%).

The results show a clear increase in MEP over time in contrast to PEF values in which no change was seen. The increase of MEP as a result of EMST is consistent with both biological rationale and former findings. Baseline MEP scores were higher than predicted for eight out of ten participants when compared with reference values for healthy adults. No normative MEP values for TL patients are found. The higher than expected MEP scores might be the effect of frequent coughing and forced expectoration which is present after TL. The high MEP values are in contrast with the study of Hutcheson et al., in which head and neck cancer patients suffering from chronic aspiration were included. Their group showed reduced average MEPs at baseline. Palmer et al. reported a good MEP at baseline in their group after partial laryngectomy and reasoned their candidates must have good pulmonary support to tolerate some amount of aspiration during recovery.
We observed no changes over time for PEF outcomes. Contrary to the MEP scores, baseline scores were lower than predicted for seven participants compared with reference values. No normative values for PEF in TL patients are found. In the group of partial laryngectomy patients performing EMST a significant increase in peak cough flow (L/min) was found, from below normal prior to the intervention to within normal range after training. Peak expiratory flow rate also increased significantly with training in a group of elderly. It is worth questioning why MEP values did not improve in the studied group of TL participants. A possible reason is impaired cough technique. As there is no glottic closure, the higher built up pressure does not lead to increased flow. Besides, no special attention was paid at the exhaling technique (ie, generating the force primarily using the rectus abdominis muscle, and keeping the thorax maximally expanded during the first part of the forced expiration) during the training.

The increase in MEP and vocal range in dB did not lead to an improvement in the clinical relevant outcome measures regarding pulmonary function, physical exertion, fatigue, and vocal functioning. It was disappointing to see that no clinically relevant benefits were found in the self-reported outcome measures. This might be the result of a sample of relatively fit TL participants which showed high baseline values in MEP and who mentioned no specific pulmonary complaints. Despite an improvement in loudness, related to the dynamic range in dB after 4 weeks of training, no changes in self-reported vocal functioning (VHI-10) were seen.

Although this pilot study offered useful insights, there are some limitations which should be mentioned related to the included group, use of EMST device and performance of training and measurements. Because of the small number of participants the results of this first EMST study in a TL group must be interpreted with caution. The outcomes cannot be generalized to the entire TL population. In particular, because the participants in our sample were all male, all fluent tracheoesophageal speakers, and relatively fit from the start, they may have progressed less and perceived less benefit, compared to what might be expected from TL patients who are less fit and report explicit coughing problems. Participants who achieved a MEP-score above 187.5 cmH2O continued the training with the device set at the maximum work load of 150 cmH2O. It remains unclear if the increase in MEP would have been even larger in case of training with an EMST device with a wider range. To measure the effect of EMST with manometry, spirometry and CPET, adjustments were needed for use on the tracheostoma. Problems creating an airtight seal and plugging the voice prosthesis and the resulting air leakage could have influenced the results of the training and the measured outcomes negatively. VHI-10, SFQ, CCQ, and Borg scales were best available questionnaires, although not specifically validated for TL populations, and should therefore be interpreted with caution.

For future research, it should be considered to test EMST in a group of TL participants without plugging the voice prosthesis prior to the training. If this also results in improvements, users can be spared the hassle of plugging. Next to this, special attention should be given towards exhaling technique used during the training. It is recommended to assess effectiveness of the training in a large group of participants which includes patients who explicitly report pulmonary problems, less fit elderly participants, and women. Finally, there are still unanswered questions about the association between patients characteristics (eg, time since TL, flap reconstruction, neck dissection etc.) and effectiveness of EMST.

Conclusion

This pilot feasibility study indicates that an EMST program is generally safe and feasible in individuals following TL, although it requires adjustments of the device and skills of the participants to perform the training. Compliance to the training program was high. The EMST leads to an increase MEP, no evident changes in PEF outcomes were found. An increase in dynamic range in dB was seen, but this did not result in less reported voice handicap measured with VHI-10. No effects were found in the voice parameters MPT and vocal range in Hz, and ventilatory efficiency during exercise. For this relatively fit group of TL participants, clinical relevant benefits measured with self-reported clinical outcomes could not be determined. It is recommended to assess EMST in a less fit TL population who specifically report pulmonary problems to further investigate potential clinical benefit.

Acknowledgments

The authors acknowledge Atos medical (Malmö, Sweden) for their research grant, which contributes to the existing infrastructure for quality of life research of the Department of Head and Neck Oncology and Surgery. The authors acknowledge Aspire Products for providing EMST training devices free of charge to study participants. FJM Hilgers, emeritus professor and emeritus head and neck surgeon at the Netherlands Cancer Institute and University of Amsterdam is greatly acknowledged for his innovative idea, enthusiasm, and support to test EMST in total laryngectomy patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Netherlands Cancer Institute receives a research grant from Atos Medical (Malmö, Sweden), which contributes to the existing infrastructure for quality of life research of the Department of Head and Neck Oncology and Surgery. Aspire Products (Atlanta, USA) provided all EMST training devices free of charge to study participants. The funders, Atos Medical and Aspire Products, had no involvement in the study design, analysis, or writing of the manuscript. The authors have no other funding, financial relationships, or conflicts of interest to disclose.

ORCID iD

Anne F. Kornman https://orcid.org/0000-0003-0004-1868

References