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Reference:

Baert Isabel, Lluch E., Mulder T., Nijs Jo, Noten Suzie, Meeus Mira.- Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review

Osteoarthritis and cartilage / Osteoarthritis Research Society - ISSN 1063-4584 - 24:2(2016), p. 213-223

Full text (Publishers DOI): http://dx.doi.org/doi:10.1016/j.joca.2015.09.002

Does pre-surgical central modulation of pain influence outcome after total knee replacement?

A systematic review

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Running headline

Does central pain modulation influence outcome after TKR?

ABSTRACT

Objective. The aim of this study is to systematically review whether the presence of altered central pain modulation pre-surgical influences outcome after total knee replacement (TKR) in patients with knee osteoarthritis (OA), and if so which indices of central pain modulation predict poor outcome after TKR.

Methods. To identify relevant articles, PubMed and Web of Science were searched. The search strategy was a combination of key words related to "Knee Osteoarthritis and Total Knee Replacement", "Central Pain Modulation" and "Post-Surgical Outcome Measures". Articles fulfilling the inclusion criteria were screened for methodological quality and results were analyzed and summarized.

Results. Sixteen prospective cohort studies were included. Strong evidence is available that presence of catastrophic thinking and poor coping strategies predict more pain after TKR and that there is no association between fear of movement and post-surgical pain or function. Evidence on other psychosocial influences is limited or conflicting. Literature on the influence of other signs of altered central pain modulation on post-surgical outcome is scarce. It is plausible that pre-surgical signs of altered central pain modulation, such as joint pain at rest or widespread pain sensitization, predict more post-surgical pain.

Conclusions. Surgeons should be attentive for patients with signs of altered central pain modulation before surgery as they might be at risk for unfavourable outcome. A broader therapeutic approach aiming to desensitize the central nervous system can be adapted in these patients. Further research is however needed to identify the influence of central pain modulation pre-surgical in predicting outcome after TKR.

Keywords: Knee osteoarthritis – central pain modulation – total knee replacement – systematic review – post-surgical outcomes

INTRODUCTION

Knee osteoarthritis (OA) is predominantly characterized by persistent pain, leading to significant disability and loss of quality of life (QoL)[1-3]. It implies enormous costs at both individual and societal levels[1, 2]. Total knee replacement (TKR) surgery is the most common surgical treatment for knee OA[4].

Even though a TKR is an effective surgical treatment for end-stage knee OA and the majority of patients with knee OA report significant pain relief and functional improvement post-surgical[5], literature shows that up to 20% of patients undergoing a TKR are dissatisfied post-surgical and complain of persisting pain, functional disability and poor QoL[6].

For TKRs, revision rates are estimated at about 6% after five years and 12% after ten years[7]. Unfortunately, even after revision, some patients still keep complaining of persisting pain[8]. Compared with primary TKR surgery, after revision reduced function, poorer QoL and higher pain intensity has been shown[9]. Furthermore, revision surgery for persisting pain of unknown origin was shown to generate inferior results when compared with revision for a well-defined reason[10-12].

Several factors can account for dissatisfaction after TKR surgery. For instance, causes can be structural/anatomical, such as infection or malpositioning. In that case, improvement in surgical procedures or aftercare could lead to better outcomes. However, patients' characteristics and expectations also seem to be important determinants of outcome following TKR[13].

Scientific understanding of chronic pain has increased substantially over the past decades and it is now well established that the biomedical model falls short in explaining many chronic musculoskeletal pain conditions[14]. Historically, according to the traditional biomedical model, OA-related pain has been considered a nociceptive pain, directly associated to the degree of structural joint damage. However, similar to other chronic pain conditions (i.e. whiplash associated disorders[15], rheumatoid arthritis[16]), there is growing body of research suggesting that in a subgroup of patients with knee OA (particularly those with moderate to severe symptomatic OA[17]), the clinical picture is dominated by sensitization of central nervous system pain pathways (i.e. altered central pain modulation) rather than by structural dysfunctions causing nociceptive pain (reviewed by Lluch Girbes et al.[18]).

Altered central pain modulation encompasses impaired functioning of brain-orchestrated descending anti-nociceptive (inhibitory) mechanisms[19], and (over)activation of descending and ascending pain facilitatory pathways[20, 21]. The net result is augmentation rather than inhibition of nociceptive transmission. In addition to the switch in balance between inhibitory and facilitatory pathways, altered central pain modulation entails altered sensory processing in the brain[21].

Consequently, altered central pain modulation is obviously related to biopsychosocial factors. Enhanced pain facilitation may be (partly) due to 'cognitive emotional modulation'[22], which refers to the capacity of forebrain centers to exert powerful influences on various nuclei of the brainstem, including nuclei identified as the origin of descending facilitatory pathways[23]. Activity in descending pathways can be modulated, for example, by forebrain products such as cognitions, emotions, attention and motivation. Several psychosocial variables (i.e. pain catastrophizing, high level of depression, anxiety, pain-related fear of movement) have indeed been suggested as negatively influencing OA-related pain and disability[24].

Given the significant role of altered central pain modulation in a subgroup of patients with knee OA[17, 18], it is not surprising that surgical interventions such as TKRs do not guarantee complete pain reduction or functional recovery, causing huge emotional and functional impact on patients and high medical and societal costs. This underscores the need for a better understanding of the role of central pain modulation in predicting outcome after TKR.

The aim of the present study is to systematically review whether the presence of altered central pain modulation pre-surgically influences outcome after TKR in patients with knee OA, and if so which indices of central pain modulation predict poor outcome. Both direct and indirect pain biomarkers related to central pain modulation were considered. Although central pain modulation and psychosocial factors do not necessarily evaluate the same construct, we included the indirect psychosocial variables as they have been recently considered as additional signs for diagnosis of altered central pain modulation[25].

METHODS

This review is reported following the PRISMA-guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[26].

Eligibility criteria

To be included in the systematic review, articles had to report results of studies that evaluated the influence of pre-surgical biopsychosocial measures of central pain modulation (I) on post-surgical outcome measures, such as pain, functional ability and QoL (O) in patients diagnosed with end-stage knee OA awaiting TKR surgery (P). All study designs except reviews and meta analyses were allowed (S).

Information sources and search strategy

To identify relevant articles PubMed (http://www.ncbi.nlm.nih.gov/entrez) and Web Of Science (http://www.sciencedirect.com/) were searched by 2 researchers (TM and IB) up to December 2014. Three groups of key words were stipulated related to "Knee Osteoarthritis and Total Knee Replacement (P)", "Central Pain Modulation (I)" and "Post-Surgical Outcome Measures (O)". Key words from these groups were combined. Relevant hand searched articles were also included to obtain as complete information as possible. The construct of the search strategy is presented in Table 1.

[Table 1]

Study selection

Two reviewers (TM and IB) screened the studies and articles were eligible if they fulfilled the following criteria:

- Study subjects were patients with knee OA awaiting TKR;
- The purpose of the study was to examine the influence of *pre-surgical* biopsychosocial indices of central pain modulation (direct and indirect pain biomarkers) on *post-surgical* outcome;
- Study designs had a minimum follow-up period of 6 weeks;

- Articles were original studies published in full text record in English, French, Dutch or German.

First, all search results were screened based on title and abstract. The full-text article was retrieved if the citation was considered potentially eligible and relevant. In the second phase, each full text article was again evaluated whether it fulfilled all criteria. If any of the eligibility criteria were not fulfilled, the article was excluded. Disagreements on inclusions between the researchers were resolved by discussion, and a final decision of a third reviewer (MM) was not necessary.

Qualification of searchers / raters

Literature was independently searched and screened by TM and SN, Masters in Physiotherapy and Rehabilitation Sciences, and IB, PhD, and trained by MM. MM obtained the degree of PhD with a dissertation regarding chronic pain and central pain modulation and published several systematic reviews in this domain.

Data items and collection

TM and IB extracted information from each included study about: (1) studydesign and purpose; (2) characteristics of study population; (3) measured variable(s) of central pain modulation pre-surgery and method of assessment; (4) post-surgical outcome variable(s) regarding pain, function and QoL and assessment method and (5) most important results for this review.

Risk of bias in individual studies

Risk of bias of the different studies was assessed using a checklist for cohort studies, provided by the Dutch Institute for Healthcare Improvement (CBO). Each question was answered using 'yes'(+), 'no'(-) or 'unclear'(?). The sum of all positively scored items, provided a total score for each study, transformed into a percentage. Studies with methodological quality lower that 50% were excluded. The overall level of evidence for each pre-surgical predictor was also rated with the Evidence-Based Guideline Development (EBRO) approach, an initiative of the Dutch Cochrane Center and the Dutch Institute for Healthcare Improvement (www.cbo.nl). In accordance with this methodology, selected

papers were classified according to their methodological quality and strength of evidence: A1: systematic review including at least two independent A2- level studies; A2: prospective cohort study of substantial size and sufficiently long follow-up period, adequate control of confounders and minimal chance of selective drop-out during follow-up; B: prospective cohort study, but not having all characteristics of an A2 stud, or a retrospective cohort study or case-controlled trial; C: non-comparative study; and D: expert opinion.

Methodological quality was assessed independently by 2 researchers (SN and IB), who were blinded from each other's assessment. Results of both researchers were compared and differences were analyzed. In case of disagreement, the reviewers screened the manuscript a second time to obtain consensus. When consensus could not be reached a third opinion was provided by the final author (MM).

Finally, results were analysed by IB to group potential predictors and outcome measures, and existing evidence regarding the influence of pre-surgical central pain modulation on poor post-surgical outcome was summarized. Methodological quality of studies was taken into account. Conclusions were classified in 4 levels. Level 1: conclusion based on one A1 study or on at least two independent A2 studies; level 2: conclusion based on one A2 study or on at least two independent B studies; level 3: conclusion based on one B or C study, and level 4: conclusion based on expert opinion only.

RESULTS

Study selection

Figure 1 shows the selection process of this review. Sixteen articles were included in the qualitative synthesis. Most studies were excluded based on predictors' nature or on the population studied.

[Figure 1 [26]]

Methodological quality assessment

Results of the risk of bias assessment are presented in Table 2. There was 87.5 % agreement (112 of 128 items) between the two researchers. After a second review and comparison of the 16 differences, reviewers reached consensus for 14 items. The remaining 2 points were solved after obtaining a third opinion. For the question regarding the follow-up duration, the minimum follow-up period was set at 3 months as this was considered the transition from the (sub)acute to the chronic post-surgical phase[27, 28]. As we included all studies with a minimum follow-up of six weeks to make the search as complete as possible, studies with a follow-up period of less than 3 months were included in the review but lost a point on methodological quality.

None of the studies had a methodological quality score lower than 50%, therefore no studies were excluded. On average, the quality of the 16 studies was 71%. Studies often lost points as result of inappropriate description of the study population and/or high chance of selection bias. The major concern for almost all studies was that both predictor measures and outcome measures were self-reported measures (questionnaires), precluding blinding. In some studies selective drop out during follow-up could not be ruled out[29, 30]. In three studies[31-33] statistical analysis were not appropriate for the study purpose (no control for confounders) or statistics were not adequately described.

Study characteristics

Characteristics of the 16 studies are presented in Table 3. All studies were prospective cohort studies. Two studies[27, 34], four studies[32, 35-37] and two studies[28, 38], respectively, were interrelated, which was taken into account when interpreting the study findings according to the EBRO approach. The number of patients ranged from 43[39] to 241[29] and the follow-up period after surgery ranged from 6 weeks[35] to 5 years[34].

Fourteen studies evaluated influences of central pain modulation on **post-surgical outcome** measure ***pain***[27-30, 32, 34-42], ten on ***function***[27, 29, 31, 34-37, 41-43] and one on ***QoL***[42]. Various questionnaires were used to obtain post-surgical outcome. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was the most commonly used questionnaire to measure pain, function and QoL.

In 14 of the 16 studies the evaluated measures of central pain modulation as **potential predictor** were ***psychosocial variables***, in the context of 'cognitive emotional modulation' [27-29, 31, 32, 34-39, 41-43]. The five most frequently evaluated psychological features were depression, anxiety, pain catastrophizing, fear of movement and coping strategy. Other psychological influences such as social support[29], stress[27], locus of control[29, 38, 43], perceived injustice[37] and illness perception[43] were investigated to a lesser extent. In order to give the reader a comprehensive overview, only the five most-often evaluated psychological features are reported, analyzed and discussed. To examine the influence of depressive symptoms (including psychological distress) on post-surgical outcome, standardized questionnaires, such as the Beck Depression Inventory, were used. The influence of anxiety was measured by various questionnaires, such as the State-Trait Anxiety Index and the Spielberger Stait Trait Anxiety Inventory and the role of pain catastrophizing as a predictor was evaluated mainly using the Pain Catastrophizing Scale. All studies investigating the role of pain-related fear of movement in the prediction of pain or knee function after a TKR used the Tampa Scale for Kinesiophobia.

In one study pre-surgical ***clinical manifestations of altered central pain modulation*** were examined as potential predictive factor[40]. This study investigated whether separate assessments of pre-surgical pain at rest and on movement could be predictive for pain after TKR. The authors assumed that joint pain at rest is caused by both central and peripheral sensitization and joint pain on movement is a

result of peripheral sensitization. So, the presence of joint pain at rest was interpreted as reflecting altered central pain modulation[40], although this assertion may not be completely correct, given the fact that rest pain may also be caused by rather peripheral joint related factors (eg. grade of inflammation, synovitis etc.).

Two studies evaluated the role of altered central pain modulation in predicting TKR outcomes by performing ***Quantitative Sensory Testing (QST)***[30, 40]. Electrical sensation, pain thresholds, pressure pain thresholds (PPTs) and hot pain thresholds (HPTs) were measured at body sites locally and distantly from the affected knee joint to evaluate localised and widespread pain sensitization, respectively.

Evidence for influence of pre-surgical altered central pain modulation on post-surgical outcome

Results are structured into three aspects of central pain modulation. To allow deeper interpretation and translation of the results, conclusions and quality of evidence of the most important results are summarized in Table 4.

1. Psychosocial influences – cognitive emotional modulation

Three studies showed that patients with pre-surgical **depressive symptoms** have significantly more *pain* complaints six months[29] or one year after surgery[27, 39]. In contrast, seven studies showed that depression, despite its association with chronic post-surgical pain in univariate analyses, had no independent unique impact on post-surgical pain at six weeks[35], three months[28], six months[29, 41], one year[36, 42] or 5 years[34] after surgery in multivariate analyses.

Five studies found significantly worse knee *function* three months[31], six months[29], one year[31, 42, 43] or five years after surgery[34] related to the presence of depressive symptoms before surgery. In contrast, three studies showed that pre-surgical depression had no unique contribution to poor knee function 6 weeks[35], 6 months[41] or 12 months[36] following surgery.

Only one study analyzed the effect of pre-surgical psychological distress on changes in *QoL* after TKR and showed that patients with pre-surgical depressive symptoms had a significantly worse QoL one year after surgery[42].

Seven studies evaluated the influence of **anxiety.** Three studies did show that patients with pre-surgical anxiety have significantly more *pain* three months[28] or one year[27, 38] after surgery. However, the opposite was found in three other studies which did not identify pre-surgical anxiety as unique predictor for more pain at 6 months[29, 41] or five years[34] after surgery.

One study showed that high pre-surgical anxiety was associated with worse *knee function* one year post-surgery[43], while others showed no significant impact on knee function at six months[41] or five years[34].

The role of **pain catastrophizing** as predictor of outcome following TKR was evaluated in seven studies. Six studies found that high levels of pain catastrophizing was a significant psychological predictor for more *pain* at six weeks[35], 3 months[28], 6 months[41], one[36, 39] or two years[32] post-surgery. Only one study showed that pain catastrophizing was not a significant predictor of post-surgical pain[37]. However, this study did find that pain catastrophizing contributed significant unique variance to the prediction of *knee function* one year post-surgery, which was also found by Sullivan et al.[36]. In contrast, two studies did not find a significant association between pain catastrophizing and post-surgical knee function[35, 41].

Four studies investigated the role of pain-related **fear of movement** in the prediction of *pain* or *knee function* after TKR[35-37, 41]. Results of these studies showed that fear of movement did not have significant influence on post-surgical *pain* or *knee function* six weeks[35], six months[41] or one year[36, 37] after surgery. It is important to mention that three of the four studies were interrelated[35-37].

Two studies investigated the role of **coping strategies** in predicting *pain* and *knee function* after TKR[29, 38]. Less problem-solving coping and more dysfunctional coping was associated with more pain and worse knee function 6 months post-surgery[29]. Passive coping independently predicted the presence of pain at 12 months post-surgery[38].

*In conclusion, strong evidence is available that the presence of **catastrophic thinking** and **poor coping** strategies predict more pain after TKR and that there is no association between fear of movement and post-surgical pain or knee function (conclusion strength 1).*

*Limited evidence was found for an influence of **depression** on post-surgical QoL and for **coping strategies** on post-surgical knee function (conclusion strength 3).*

There is conflicting evidence for the role of depressive symptoms and anxiety in predicting pain and knee function post-surgery, as well as for the role of pain catastrophizing in predicting knee function (conclusion strength 3).

2. Clinical manifestations of altered central pain modulation

One study tested whether separate assessments of pain at rest and on movement could be of value in predicting the effect of TKR on *pain* 18 months post-surgery in 69 OA patients[40]. The researchers assumed that pain at rest is more linked to sensitization of nerve terminals in the dorsal horn and spinal cord neurons, reflecting altered central pain modulation, in contrast to pain triggered by movement. A significant less favorable outcome in terms of pain relief was observed for patients with high pre-surgical VAS score for pain at rest[40]. Nevertheless, pain at rest may, in our opinion, also be caused by rather structural non-central factors in the joint itself.

3. Quantitative Sensory Testing

Two studies used QST measurements to explore the relationship between pre-surgical pain thresholds and chronic *pain* one year[30] and 18 months[40] after TKR. Different pain thresholds were measured (PPT[30], HPT[30] and electrical pain thresholds[40]) at the index knee[30], hand[40] or forearm[30] to allow testing of localized pain sensitization and widespread pain sensitization. Results showed that signs of pre-surgical widespread pain sensitization, measured using pressure algometry[30] or electrical stimulation[40], are associated with more pain after TKR.

*It is plausible that **pre-surgical signs of altered central pain modulation**, such as joint pain at rest or widespread pain sensitization, predict more pain after a TKR. However, further study into this topic is required.*

DISCUSSION

The goal of this systematic literature search was to review the literature investigating the influence of pre-surgical indices of central pain modulation on post-surgical outcome measures in patients with end-stage knee OA awaiting TKR surgery.

1. Psychosocial influences – cognitive emotional modulation

Traditional understanding of OA-related pain has recently been challenged in light of scientific evidence supporting a key role of altered central pain modulation in a subgroup of this population[44]. In the context of 'cognitive emotional modulation', some psychosocial variables seem to play a significant role. Results of this review show that high pre-surgical levels of pain catastrophizing and poor pain coping strategies predict post-surgical pain, which is consistent with cognitive behavioural pain models suggesting that negative appraisals of pain (e.g. catastrophic thinking) will influence the intensity and persistence of a person's pain experience. Pain catastrophizing can interfere with descending pain-inhibitory systems and might facilitate neuroplastic changes in the spinal cord during repeated painful stimulation, subsequently promoting sensitization in the central nervous system[24, 45]. Although influence of pain-related fear of movement on post-surgical knee function may have been expected, a reasoning supported by the fact that pain-related fear would lead to activity avoidance (fear-avoidance model)[46, 47], strong evidence was found for no unique contribution of fear of movement to knee function. For other psychosocial factors, such as depression or anxiety, only limited or conflicting evidence was found.

It is important to mention that the heterogeneity of the studied psychosocial predictors and outcome measures could limit the level of certainty of our conclusion. For example, depression was measured in different ways, using the Beck Depression Inventory[27, 28, 34, 38], the Patient Health Questionnaire-9[35], the Patient Health Questionnaire-8[41], the Center for Epidemiological Studies Depression Scale[39], the Depression, Anxiety and Stress Scale[29] and the Hospital Anxiety and Depression Scale[42, 43]. The wide variability makes it difficult to compare results of different studies. Moreover, the follow-up period

after surgery ranged from 6 weeks to 5 years, which can have considerable influence on the results. Future research should aim for more homogeneity within studies in order to achieve stronger evidence.

In addition, patient populations varied across studies and patient characteristics were different within studies, which may have also influenced measurements and results. Studies should use multivariate analyses and control for the most important confounders. In some studies, important confounders were not taken into account or this was not adequately described[31, 32]. In other studies[27-29, 34-39, 41-43] confounders were taken into account, but the nature of the confounders differed, which complicates comparison.

2. Clinical manifestations of altered central pain modulation & 3. Quantitative Sensory Testing

In addition to psychological factors, literature about the role of other indices of central pain modulation is scarce[30, 40]. Reporting a high pre-surgical VAS score for joint pain at rest seems to be a risk factor for poor outcome after TKR[40]. It is however questionable to consider joint pain at rest definitely as a reflection of altered central pain modulation. Pain at rest is often related to the grade of inflammation and can therefore also be explained by other potential factors, such as presence of Bone Marrow Lesions or effusion/synovitis. Therefore, it is important to interpret this factor as being suggestive, as a feature that *may* reflect a central pain modulation mechanism. In addition, a low pre-surgical pain threshold in response to application of an electrical[40] or pressure stimulus[30], seems to be associated with less favourable outcome following TKR. These features are assumed to be involved in altered central pain modulation [48-50]. It is important to mention that in the study of Wylde et al.[30], the sample size was relatively small with consequently limited statistics (no control for possible confounders). This exploratory study stresses the need for further research into this area. Large population studies, in which other known risk factors are assessed and controlled for, are needed to establish the role of pre-surgical measures of central pain modulation in predicting outcome after TKR.

It could be expected that in a subgroup of OA patients awaiting TKR surgery with signs of altered central pain modulation, local application of different modalities of treatment, including TKR surgery, will not always be followed by amelioration or complete resolution of symptoms, as there is no clear relation between peripheral input and perceived pain. It has been shown that lowered pain thresholds may return to normal after TKR[51], but there is also experimental support from animal studies for persistence of altered central pain modulation even after complete resolution of tissue damage[52], so this issue is ambiguous. In studies of Lundblad et al.[40] and Wylde et al.[30], QST measurements were not repeated post-surgery, so this warrants further investigation.

In spite of the limitations, this review has important implications for clinical practice. Increased attention to a biopsychosocial approach in orthopaedic surgery, specifically TKR, seems to be very important and may lead to better outcomes. If individuals at risk for post-surgical pain and disability may be identified early, individual's suffering could be prevented or reduced to a significant degree. Patients awaiting TKR should be screened for signs of altered central pain modulation. In particular, attention should be directed to pain catastrophizing and pain coping strategies, which are easy to assess using the Pain Catastrophizing Scale[53] and Pain Coping Inventory[54], respectively. High levels of pain at rest can be monitored as well using pain rating scales. In addition, pain thresholds can easily be measured evaluating the presence of widespread pain sensitisation as sign of altered central pain modulation.

The results of this review can argue for peri-surgical interventions addressed to patients with signs of altered central pain modulation, such as cognitive-behavioral therapy (graded activity and graded exposure) or therapeutic pain neuroscience education, in particular patients with catastrophic thinking, poor coping strategies, high joint pain at rest and low pain thresholds. Evidence supports the use of these interventions for patients with chronic musculoskeletal pain[55-57], but its use for patients awaiting TKR surgery has been suggested[18], but not yet studied.

Although prevalent in chronic OA pain, altered central pain modulation is not present in every patient[58]. It has been argued that some individuals may be predisposed to altered central pain

modulation irrespective of the degree of OA, so at least some degree of sensitization might be a trait rather than a state[59]. Recently, specific classification criteria to assist clinicians on differentiating between neuropathic, nociceptive and central sensitization pain have been published[25]. In patients where altered central pain modulation is dominant, a broader therapeutic approach aiming to desensitize the central nervous system could be adapted (first).

In conclusion, as the economic impact of severe, unexplained pain after TKR is profound, surgeons should be attentive for patients with signs of altered central pain modulation before surgery as they might be at risk for unfavourable outcome after TKR. A broader therapeutic approach aiming to desensitize the central nervous system can be adapted in these patients. Further research is needed to identify the role of central pain modulation in predicting outcome after TKR and to address questions concerning the effectiveness of interventions that target different aspects such as the central nervous system, in contrast to therapeutic modalities only directed to structural knee joint pathology.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of this study. IB and TM contributed to the analyses of the data. All authors contributed to the interpretation of the data. Article drafts were written by IB and critically revised by all authors. The final version of the article was approved by all authors. IB takes responsibility for the integrity of the work as a whole (isabel.baert@uantwerpen.be).

ROLE OF THE FUNDING SOURCE

This study was not financially supported.

COMPETING INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

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