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The influence of sleep quality on preoperative risk factors associated with chronic postoperative pain after knee and hip arthroplasty

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Manuscript ID	BJP-20-0093
Manuscript Type:	Original Manuscript
Keywords:	Sleep quality, Preoperative risk factors, Total knee and hip arthroplasty, Postoperative pain, Pain catastrophizing, Depression
Abstract:	<p>Background: Chronic postoperative pain following total joint replacement (TJR) is a substantial clinical problem and preoperative predictive risk factors such as high levels of anxiety and depression have been identified. Poor sleep seems to affect several cognitive factors, but it is currently unclear how sleep quality is associated with preoperative predictive risk factors for chronic postoperative pain. This exploratory cohort study investigated 1) the relationship between preoperative sleep quality, clinical pain intensity, pain catastrophizing, anxiety, and depression, and 2) their associations to chronic postoperative pain following TJR.</p> <p>Methods: Preoperative Pittsburgh Sleep Quality Index (PSQI), Pain Catastrophizing Scale (PCS), and Hospital Anxiety and Depression Scale (HADS) were obtained from 74 knee and 89 hip osteoarthritis (OA) patients scheduled for TJR. Pain intensity at rest was assessed before and 12 months after TJR using a visual analog scale (VAS). Poor sleepers were identified preoperatively as patients with PSQI scores higher than 5.</p> <p>Results: Poor sleepers demonstrated higher preoperative VAS ($p=0.003$), higher pain catastrophizing ($p<0.001$), higher anxiety ($p<0.001$) and depression ($p<0.001$) when compared to good sleepers. Preoperative VAS was correlated with preoperative factors PSQI ($r=0.36$, $p<0.001$), PCS ($r=0.46$, $p<0.001$), and depression ($r=0.23$, $p=0.004$), and postoperative VAS ($r = 0.32$, $p < 0.001$).</p> <p>Conclusion: OA patients with poor preoperative sleep quality show higher preoperative pain intensities, higher scores of pain catastrophizing, and depression. High preoperative pain intensity, but not sleep quality, was associated with higher chronic postoperative pain intensity. Future studies are encouraged to further explore the associations between sleep and chronic postoperative pain.</p> <p>Clinicaltrials.gov (identifier number: NCT02405104)</p>

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Abstract

Background: Chronic postoperative pain following total joint replacement (TJR) is a substantial clinical problem and preoperative predictive risk factors such as high levels of anxiety and depression have been identified. Poor sleep seems to affect several cognitive factors, but it is currently unclear how sleep quality is associated with preoperative predictive risk factors for chronic postoperative pain. This exploratory cohort study investigated 1) the relationship between preoperative sleep quality, clinical pain intensity, pain catastrophizing, anxiety, and depression, and 2) their associations to chronic postoperative pain following TJR.

Methods: Preoperative Pittsburgh Sleep Quality Index (PSQI), Pain Catastrophizing Scale (PCS), and Hospital Anxiety and Depression Scale (HADS) were obtained from 74 knee and 89 hip osteoarthritis (OA) patients scheduled for TJR. Pain intensity at rest was assessed before and 12 months after TJR using a visual analog scale (VAS). Poor sleepers were identified preoperatively as patients with PSQI scores higher than 5.

Results: Poor sleepers demonstrated higher preoperative VAS ($p=0.003$), higher pain catastrophizing ($p<0.001$), higher anxiety ($p<0.001$) and depression ($p<0.001$) when compared to good sleepers. Preoperative VAS was correlated with preoperative factors PSQI ($r=0.36$, $p<0.001$), PCS ($r=0.46$, $p<0.001$), and depression ($r=0.23$, $p=0.004$), and postoperative VAS ($r = 0.32$, $p < 0.001$).

Conclusion: OA patients with poor preoperative sleep quality show higher preoperative pain intensities, higher scores of pain catastrophizing, and depression. High preoperative pain intensity, but not sleep quality, was associated with higher chronic postoperative pain intensity. Future studies are encouraged to further explore the associations between sleep and chronic postoperative pain.

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4 **Keywords:** Sleep quality; preoperative risk factors; total knee and hip arthroplasty; postoperative pain;
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6 pain catastrophizing; depression
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For Peer Review

Introduction

Knee and hip osteoarthritis (OA) are highly prevalent musculoskeletal disorders that affect the elder population.¹ The treatment for end-stage-OA is total joint replacement (total knee or hip replacement: TKR and THR, respectively), however, it is well-established that an approximate 20% of patients following TKR and 10% of patients following THR will report chronic postoperative pain.²

Preoperative pain intensity³ and cognitive factors such as high preoperative pain catastrophizing predicts the presence of chronic postoperative pain six and 24 months after TKR.⁴⁻⁸ In a mixed musculoskeletal pain cohort, improvements in depression, anxiety, and pain catastrophizing predicted pain 12 months after being enrolled in a telecare rehabilitation program.⁹ Additionally, insomniac knee OA patients exhibit stronger signs of central sensitization, and pain catastrophizing may attain a key role in moderating sleep efficiency and the development of pain sensitization.¹⁰ A recent study demonstrated that preoperative sleep parameters such as Pittsburgh Sleep Quality Index (PSQI) and daily sleepiness were associated with acute postoperative pain after TKR and THR.¹¹ Sleep may therefore play an important role in body homeostasis and in mediating cognitive factors known to be involved with postoperative chronic pain, possibly through a bidirectional relationship with e.g. anxiety and depression.¹² Conclusively, these studies indicate that there might be an interplay between cognitive factors, sleep and postoperative pain. However, no evidence is currently available on how preoperative poor sleep is associated with preoperative risk factors pain catastrophizing, depression, anxiety, or chronic postoperative pain 12 months after TKR and THR.

The aims of the present study were to 1) assess the impact of preoperative sleep quality on preoperative clinical pain intensity, pain catastrophizing, anxiety, and depression and 2) explore the associations

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4 between preoperative sleep quality, pain intensity, pain catastrophizing, depression, and anxiety to
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6 chronic postoperative pain intensity 12 months after total joint replacement in patients with OA.
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10 11 **Methods**

12 13 14 *Patients*

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17 A total of 185 knee OA patients (82 men and 103 women; mean age \pm SD: 68.8 \pm 8.92 years) and 189
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19 hip OA patients (120 men and 69 women; mean age \pm SD: 66.93 \pm 13.75 years) scheduled for TKR
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21 and THR were enrolled. The patients took part in a large randomized controlled trial assessing the
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23 effect of acute and 7 days postoperative administration of the muscle relaxant chlorzoxazone on
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25 postoperative pain (12 months after TKR or THR). Chlorzoxazone is believed to enhance acute
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27 postoperative pain recovery¹³, which may improve postoperative pain¹⁴, but the study demonstrated no
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29 effect of chlorzoxazone on acute and chronic postoperative pain compared to placebo.¹⁵ Therefore,
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31 these exploratory analyses were carried out. Patients were assessed for eligibility at a prescheduled
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33 hospital visit preceding admission for surgery between September 2015 and September 2016, and
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35 follow-up was conducted 12 months post-surgery (2017).
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41 Exclusion criteria involved use of gabapentinoids, glucocorticoids, opioids, anxiolytics, antiepileptics
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43 or antidepressants; alcohol abuse; other pain treatments outside of standard care; malignant conditions;
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45 pregnancy; BMI > 40 kg/m²; suffering from other peripheral or central acting diseases; allergy towards
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47 chlorzoxazone; perioperative complications (e.g. fractures) and liver diseases. All patients signed an
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49 informed consent prior to inclusion. The study was approved by the Danish Medicines Agency, the
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51 local ethics committee (VN-20150024) and Danish Data Protection Agency, preregistered at
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4 Clinicaltrials.gov (identifier number: NCT02405104) and conducted in accordance to the Declaration
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6 of Helsinki.
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10 11 *Sleep quality* 12

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14 Sleep quality was assessed preoperatively using the PSQI. The PSQI measures sleep quality and
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16 disturbances over 1 month intervals by 19 items including subjective sleep quality, sleep latency, sleep
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18 duration, habitual sleep efficiency, sleep disturbances, sleep medication usage, as well as daytime
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20 dysfunction and is assessed on a 0-21 point scale.¹⁶ A PSQI measure > 5 indicates poor sleep, with
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22 reported sensitivity of ~90% when distinguishing good from poor sleepers.¹⁶
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26 27 28 *Pain Catastrophizing Scale* 29

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31 The Pain Catastrophizing Scale (PCS)¹⁷ was administered preoperatively to assess pain catastrophizing.
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33 The PCS scores range from 0-52 across three subscales (rumination, magnification, and helplessness)
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35 based on 13 items (each scored from 0-4) reflecting the frequency of catastrophizing cognitions. The
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37 PCS is validated in chronic pain patients, pain-free subjects^{18,19} and the Danish version in clinical and
38
39 non-clinical cohorts.²⁰ The total PCS score was calculated and used for further analysis.
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45 *Anxiety and depression* 46

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48 The Hospital Anxiety and Depression Scale (HADS) is considered part of the (British) National
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50 Institute for Health and Care Excellence (NICE) recommendation for diagnosis of depression and
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52 anxiety²¹, and was employed to determine the level of preoperative anxiety and depression. The scale
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4 consists of 14 questions of which seven items assesses anxiety and seven items assesses depression.²²
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6 Each item is evaluated by a score from 0-3 and summated to give a separate score for anxiety and
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8 depression. Cut-off values for anxiety and depression scores are 8 or above, which yield good
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10 specificity and sensitivity.²³
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16 *Pain intensity measures*

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18 Clinical pain intensity was defined as pain after 20 minutes of rest and was rated on a visual analogue
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20 scale (VAS; 0-10 cm; referred to as pain from hereon). Both pre- and 12 months postoperative clinical
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22 pain intensity were obtained.
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28 *Statistics*

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31 First, the potential effect of chlorzoxazone on the study parameters was tested in a multivariate analysis
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33 of co-variance (MANCOVA), with fixed factor randomization (chlorzoxazone or placebo).
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36 Patients (TKR and THR pooled) were grouped based on sleep quality into good or poor sleepers
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38 defined as PSQI>5. Independent samples t-tests were conducted between the two subgroups to explore
39
40 whether the two groups differed. Chi-square tests on proportions were used to test differences in
41
42 proportions of gender and surgery type between good and poor sleepers. Associations between
43
44 preoperative pain intensity, sleep quality, cognitive factors, and chronic postoperative pain were tested
45
46 using Pearson's product-moment correlation analysis. A p-value below 0.05 was set to determine
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48 statistical significance. Bonferroni correction was applied to correct for multiple comparisons ($0.05/5 =$
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50 0.01). All statistical analyses were performed in Statistical Package for Social Sciences (SPSS; version
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52 26, IBM). Data are reported as mean \pm standard error of the mean (SEM) unless otherwise stated.
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Results

A total of 163 patients had all preoperative and postoperative data available and were included for further analysis (CONSORT diagram, Fig. 1). The excluded patient group displayed a significantly higher proportion of females (62.8%) compared with included patients (37.2%, $p = 0.03$) but otherwise no significant differences were found for age ($t_{372} = 1.68$, $p = 0.09$), PCS ($t_{328} = 0.89$, $p = 0.4$), PSQI ($t_{230} = -0.54$, $p = 0.6$), anxiety ($t_{295} = 0.31$, $p = 0.76$), or depression ($t_{291} = 0.3$, $p = 0.3$). Demographics for the included patients can be seen in Table 1. The MANCOVA demonstrated that randomization (chlorzoxazone or placebo) did not impact preoperative pain ($F_{1,161} = 1.74$, $p = 0.19$), postoperative pain ($F_{1,161} = 0.87$, $p = 0.35$), PCS ($F_{1,161} = 0.14$, $p = 0.71$), PSQI ($F_{1,161} = 0.39$, $p = 0.53$), anxiety ($F_{1,161} = 0.41$, $p = 0.52$), or depression ($F_{1,161} = 2.15$, $p = 0.14$).

[Insert Figure 1.]

[Insert Table 1.]

The impact of sleep quality on psychological factors

The good sleepers were older than the poor sleepers ($t(151) = -0.25$, $p = 0.02$). In addition, a higher proportion of females were found in the poor sleepers' group (poor sleepers = 50m/44f; good sleepers = 41m/18f) ($\chi^2 = 3.9$, $p = 0.046$). No difference was observed for proportion of surgery type in the subgroups ($\chi^2 = 3.2$, $p = 0.07$).

The poor sleepers reported significantly increased preoperative pain intensity ($t(151) = 3.06$, $p = 0.003$; Fig. 2A), higher pain catastrophizing thoughts ($t(149.16) = 4.96$, $p < 0.001$; Fig. 2B), higher anxiety

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4 scores ($t(150.88) = 5.32, < 0.001$; Fig. 2C), and higher depression scores ($t(150.51) = 4.5, p < 0.001$;
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6 Fig. 2D) compared with the good sleepers. No difference was found comparing postoperative pain
7
8 intensity between good and poor sleepers ($t(151) = 0.17, p = 0.86$).
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11 12 13 **[Insert Figure 2.]**

14 15 16 17 18 *Associations between preoperative sleep, preoperative pain intensity, and preoperative cognitive* 19 20 *factors*

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23 Preoperative PSQI was positively correlated with preoperative pain ($r = 0.36, p < 0.001$). In addition,
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25 preoperative pain intensity was positively correlated to preoperative PCS ($r = 0.46, p < 0.001$),
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27 preoperative depression ($r = 0.23, p = 0.004$), but not preoperative anxiety levels ($r = 0.16, p = 0.12$,
28
29 Bonferroni-corrected).
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32 33 34 35 *Association between preoperative sleep quality, pain intensity, cognitive factors, and postoperative* 36 37 *chronic pain*

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40 Chronic postoperative pain intensity was positively correlated with preoperative pain intensity ($r =$
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42 $0.32, p < 0.001$) and trended towards significance for preoperative PCS ($r = 0.15, p = 0.057$). There was
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44 no significant correlation between preoperative sleep quality and chronic postoperative pain ($r = 0.05,$
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46 $p = 0.52$).
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51 52 **Discussion**

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4 The current study is the first larger scale study to assess the impact of poor sleep quality on
5 preoperative and chronic postoperative pain after total joint replacement. The results show that poor
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7 sleepers demonstrate higher preoperative pain intensity, higher levels of pain catastrophizing thoughts,
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9 and higher levels of anxiety and depression. Finally, higher preoperative pain intensity, but not
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11 preoperative sleep quality, was associated with higher chronic postoperative pain intensity.
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18 *Sleep quality, its impact on preoperative pain, and relation to chronic postoperative pain*
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20 Up to 50% of chronic pain patients report poor sleep²⁴, and an earlier study reported that preoperative
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22 sleep quality mediated the relationship between 1 month postoperative pain and functional limitation 3
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24 months after surgery.²⁵ A recent systematic review and meta-analysis identified sleep difficulties as a
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26 strong preoperative predictor of poor postoperative pain control, however, this was only based on two
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28 studies.²⁶ Additionally, Mamie et al.²⁷ showed preoperative chronic sleep difficulties increased the risk
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30 of severe postoperative pain following intraperitoneal or orthopedic surgery. Poor preoperative sleep
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32 has also been shown to be associated with poor physical recovery after cardiac surgery.²⁸ A recent
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34 study reported that preoperative PSQI and daily sleepiness were associated with acute postoperative
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36 pain, up to 3 months after TKR and THR.¹¹ These findings indicate there may be an association
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38 between having poor preoperative sleep and reporting chronic postoperative pain however the
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40 mechanisms are unclear. In healthy participants, partial and total sleep deprivation have shown to affect
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42 both peripheral^{29,30} and central facilitatory and inhibitory pain mechanisms.^{31,32} These pain mechanisms
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44 are also altered in chronic pain patients suffering from e.g. fibromyalgia or knee OA^{33–36} and may
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46 predict the analgesic response to standard pain treatment in OA^{37,38} and reports of chronic postoperative
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48 pain following TKR^{39–44} and THR.^{45,46} Together with the current findings, these studies indicate that
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50 OA patients reporting poor sleep also suffer from higher preoperative pain which is predictive of
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4 chronic postoperative pain.³ Roehrs and Roth⁴⁷ demonstrated, in a cohort of 18 knee and hip OA
5 patients scheduled for TJR, that extending sleep by approx. 1 hour yielded an improvement in acute
6 postoperative pain and opiate use, indicating that improving sleep might yield better postoperative
7 outcomes for patients and more research in this field is encouraged in the future. It is important to note
8 that an earlier study demonstrated that knee OA patients scheduled for revision surgery were younger
9 than those undergoing primary surgery, and also reported higher chronic pain intensity.⁴⁸ Since the
10 current study found a difference in age between those patients who sleep poorly compared to those who
11 sleep well, the possible effect of age on postoperative pain should be considered, despite the
12 availability of contrasting evidence on the association between age and postoperative pain after various
13 surgical procedures.⁴⁹ Furthermore, a larger proportion of women was found in the poor sleep group,
14 and since women in general report higher preoperative pain intensity⁵⁰, and more frequently develop
15 chronic postoperative pain^{51,52}, this should be acknowledged and controlled in future studies.
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34 *Sleep quality and its relation to anxiety, depression, and pain catastrophizing*

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37 Sleep abnormalities have been associated with high-risk of depression^{53,54}, anxiety¹², and pain
38 catastrophizing⁵⁵. For instance, depression was shown to be independently associated with sleep
39 problems in rheumatoid arthritis patients⁵⁶, however, the direction in which insomnia, depression, and
40 even chronic pain interact remains elusive.⁵⁷ In temporomandibular disorder patients, sleep disturbance
41 was shown to exert a mediating role on pain catastrophizing.⁵⁸ In support, indirect evidence for the role
42 of sleep on pain catastrophizing was shown in another study, where cognitive behavioral therapy for
43 insomnia in knee OA patients reduced pain catastrophizing.⁵⁹
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4 Together with the current findings of higher levels of pain catastrophizing in knee OA patients who
5 report poor sleep prior to TJR, these studies support early interventions aimed at managing depression,
6 anxiety, and pain catastrophizing, since, especially the latter, is known to predict chronic postoperative
7 pain.^{4,5} A recent multi-site randomized clinical trial was performed to lower catastrophizing thoughts in
8 TKR patients but showed no effect on the incidence of chronic postoperative pain.⁶⁰ Therefore, future
9 studies may explore the possibility of managing this triad of cognitive impairment through for instance
10 sleep therapy or cognitive behavioral therapy, to evaluate its effect on chronic postoperative pain.
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22 *Cognitive factors and their relation to chronic postoperative pain*

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26 A systematic review and meta-analysis showed that preoperative anxiety and pain catastrophizing hold
27 predictive value for chronic postoperative pain 3-12 months after various surgeries.⁶¹ Another study
28 reported that patients enrolled for abdominal surgery who underwent a preoperative pain management
29 intervention for understanding and managing chronic postoperative pain, exhibited lower preoperative
30 anxiety and pain attitude, and importantly, reported lower acute pain intensity up to 24 hours after
31 surgery.⁶² In knee OA, preoperative anxiety and depression was shown to be associated with chronic
32 postoperative pain 6⁶³ and 12 months after TKR.⁶⁴ Furthermore, in TKR patients, pain intensity and
33 pain-related distress may be associated with anxiety, depression, and pain catastrophizing⁶⁵, pain self-
34 efficacy, and fear of movement.⁶⁶ In addition, preoperative pain catastrophizing has been demonstrated
35 to predict chronic postoperative pain six⁴ and 24 months⁵ after TKR, albeit controversial evidence
36 exist.⁶⁷ In this respect, poor sleep before TKR was shown to mediate the relationship between 1 and 3
37 months postoperative functional limitations.²⁵ Furthermore, depression has been shown to predict
38 higher postoperative pain whereas catastrophizing was shown to be a unique predictor of higher
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4 postoperative night time pain.⁶⁸ In populations suffering from sleep-related disorders such as sleep
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6 apnea, the prevalence of depression and anxiety is more pronounced when compared to a non-apnea
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8 group.⁶⁹ The current study adds to this growing body of evidence by showing that hip and knee OA
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10 patients reporting poor sleep, exhibit higher preoperative anxiety, depression, and pain catastrophizing
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12 levels. These factors may play a direct or an indirect role in chronic postoperative pain, and further
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14 research similar to the study by Riddle et al.⁶⁰ is needed, to further our understanding of preoperative
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16 interventions on cognitive factors associated with postoperative pain.
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22 *Limitations*

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24 The current study is limited by missing data for ~56% of the patients and a larger proportion of females
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26 were found in the excluded and poor sleepers' groups. Females are known to report higher anxiety⁷⁰,
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28 higher preoperative pain intensity⁵⁰, and more frequently develop chronic postoperative pain^{51,52} and
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30 therefore the results of the current study should be interpreted with care.
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36 **Conclusion**

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38 The current study is the first large-scale study to investigate the effect of preoperative quality of sleep
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40 on preoperative risk factors for chronic postoperative pain after TRJ. The results showed that, OA
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42 patients with poor preoperative sleep have higher preoperative pain intensities and higher levels of pain
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44 catastrophizing, anxiety, and depression compared to patients that sleep well. Preoperative pain
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46 intensity, but not sleep quality, was associated with chronic postoperative pain 12 months after total
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48 knee and hip arthroplasty. Since preoperative sleep quality affected preoperative pain, which predicted
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50 chronic postoperative pain, future studies are encouraged to investigate if improving sleep prior to
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52 surgery may reduce preoperative pain intensity to decrease the risk of chronic postoperative pain.
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22 **Data availability:** Upon request
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4 **Figures**
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6 **Figure 1. CONSORT diagramme.** Flow of patients throughout the trial and the secondary analysis
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8 conducted in the current study. *TKA: Total knee arthroplasty, THA: Total hip arthroplasty*
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13 **Figure 2. Differences between OA patients suffering from poor sleep versus good sleep.** Poor
14 sleepers reported significantly higher pain (A), pain catastrophizing thoughts (B), anxiety (C), and
15 depression (D). *PCS: Pain Catastrophizing Scale; Anxiety/Depression: Hospital Anxiety and*
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20 *Depression Scale*
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4 **Tables**
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8 **Table 1. Demographics and descriptives of the patient cohort. Mean \pm SD. PCS: Pain**
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10 *Catastrophizing Scale, PSQI: Pittsburgh Sleep Quality Index, HADS: Hospital Anxiety and*
11 *Depression Scale.*
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(N = 163)	
Age	66.71 \pm 13.63 (SD) years
Gender	99 m; 64 f
Surgical procedure (TKR/THR)	74 / 89
Preoperative pain intensity (0-10)	3.55 \pm 2.3
PCS (0-52)	17.79 \pm 12.25
PSQI (0-21)	7.91 \pm 4.61
HADS (Anxiety; 0-21)	3.96 \pm 3.36
HADS (Depression; 0-21)	2.31 \pm 2.64

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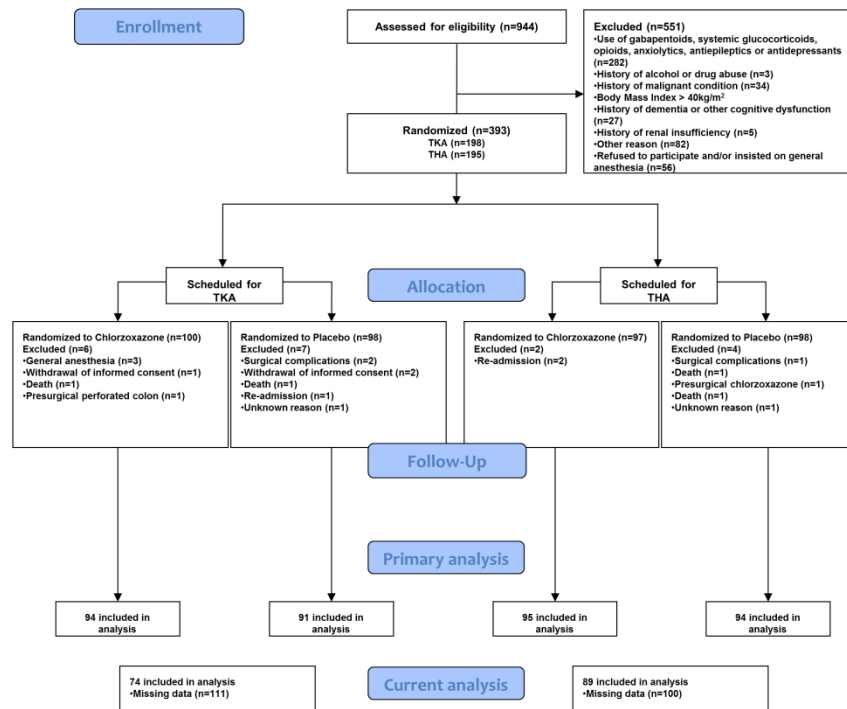


Figure 1. CONSORT diagramme. Flow of patients throughout the trial and the secondary analysis conducted in the current study. TKA: Total knee arthroplasty, THA: Total hip arthroplasty

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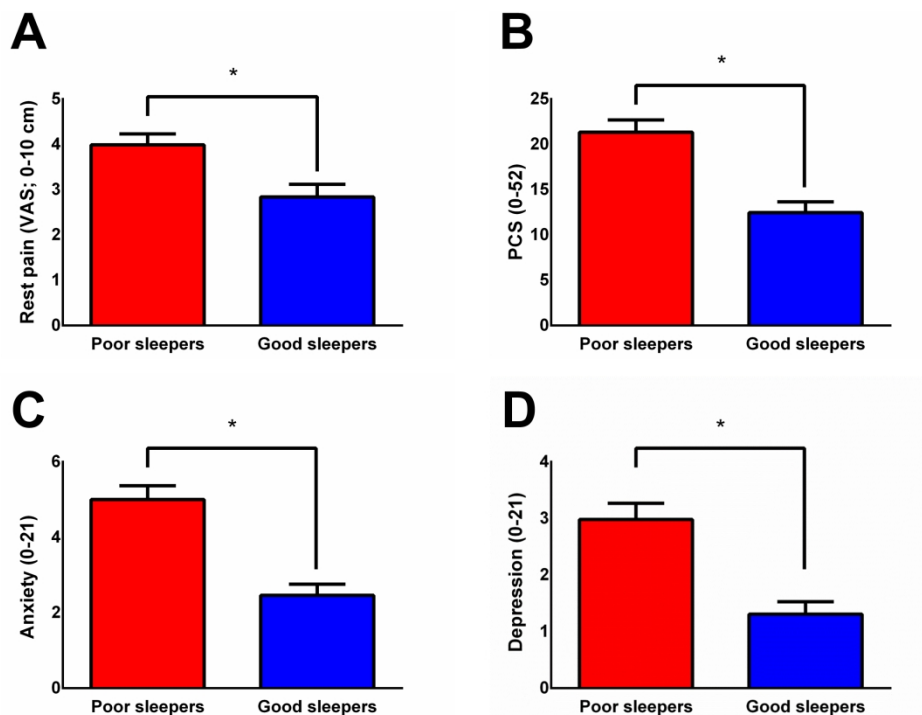


Figure 2. Differences between OA patients suffering from poor sleep versus good sleep. Poor sleepers reported significantly higher pain (A), pain catastrophizing thoughts (B), anxiety (C), and depression (D). PCS: Pain Catastrophizing Scale; Anxiety/Depression: Hospital Anxiety and Depression Scale

254x190mm (300 x 300 DPI)

Table 1. Demographics and descriptives of the patient cohort. Mean \pm SD. PCS: Pain Catastrophizing Scale, PSQI: Pittsburgh Sleep Quality Index, HADS: Hospital Anxiety and Depression Scale.

(N = 163)	
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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	N/A – secondary analysis to primary trial
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-4
	2b	Specific objectives or hypotheses	3-4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	4
	4b	Settings and locations where the data were collected	4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	4-6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	N/A
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	N/A
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	N/A
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	N/A

1	Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	N/A
2				
3	Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
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5		11b	If relevant, description of the similarity of interventions	
6				
7	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
8		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	6
9				
10	Results			
11	Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
12				
13		13b	For each group, losses and exclusions after randomisation, together with reasons	7
14	Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
15				
16		14b	Why the trial ended or was stopped	N/A
17	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
18	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
19				
20				
21	Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
22				
23		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
24	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	4
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27	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	N/A
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29	Discussion			
30	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	12
31	Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12
32	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8-12
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34	Other information			
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36	Registration	23	Registration number and name of trial registry	1 & 5
37	Protocol	24	Where the full trial protocol can be accessed, if available	5
38	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	13
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1 *We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also
2 recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials.
3 Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.
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For Peer Review