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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-093872
Article Type:	Original research
Date Submitted by the Author:	18-Sep-2024
Complete List of Authors:	Amirpour, Anahita; Karolinska Institutet, Neurobiology, Care Sciences and Society Bergman, Lina; Karolinska Institute, Neurobiology, care sciences, society Markovic, Gabriela; Karolinska Institutet, Department of Clinical Sciences; Danderyd University Hospital, Department of Rehabilitation Medicine Liander, Karin; Karolinska Universitetsjukhuset i Huddinge, Perioperative Medicine Intensive care Nilsson, Ulrica; Karolinska Institutet, Neurobiology, Care Sciences and Society Eckerblad, Jeanette; Karolinska Institute, Neurobiology, Care sciences, society
Keywords:	NEUROLOGY, ORTHOPAEDIC & TRAUMA SURGERY, Old age psychiatry < PSYCHIATRY

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Understanding neurocognitive recovery in older adults after total hip arthroplasty: neurocognitive assessment, blood biomarkers, and patient experiences - a mixed methods study.

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Acknowledgments: We thank Jennifer Kanon, Professor Lars. I Eriksson, Professor Lars Rasmussen, Professor Olav Rooijackers, Dr. Harald Brismar and all health care professionals at the hospital for their assistance. Extra thanks to the patients who participated in our study.

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Abstract:

Objective: This study aims to bridge the current knowledge gap in perioperative research on the relationship between subjective cognitive decline, neurocognitive assessment, and blood biomarkers.

Design: Mixed methods study, with a parallel convergent design. We assessed cognitive function using a neurocognitive test battery, blood biomarkers, quality of recovery, and semi-structured interviews.

Setting and Participants: The study included 40 older adult patients scheduled for total hip arthroplasty at a hospital in Sweden.

Outcome measures: Preoperatively, the patients underwent the neurocognitive test battery, blood sampling and quality of recovery assessment. Postoperatively, they were re-assessed with blood samples on days 1 to 3, and with neurocognitive tests, blood biomarkers, quality of recovery and qualitative interviews at 2 weeks.

Results: Five patients were classified with delayed neurocognitive recovery in the tests, whereas in the qualitative data most patients reported decline, mainly cognitive symptoms related to executive functions and fatigue. We found that psychological factors including sense of agency and low mood impacted cognitive recovery and daily functioning. Elevated inflammatory blood biomarkers were not detected pre- or postoperatively in patients with detected delayed neurocognitive recovery. The global score of postoperative recovery was 40.9, indicating low quality of recovery.

Conclusion: Many patients reported subjective cognitive decline but had no delayed neurocognitive recovery on the neurocognitive tests. Assessing psychological factors are influential for postoperative cognitive recovery. Future direction would benefit from longitudinal follow-ups with objective neurocognitive tests, fatigue assessment, instrumental activities in daily living and subjective reports, with a multidisciplinary team focus.

Clinical Trial Registration: NCT05361460

Keywords: postoperative cognitive complications, postoperative cognitive dysfunction, total hip arthroplasty, blood biomarkers, delayed neurocognitive recovery

Article summary

Strengths and limitations of this study

- To our knowledge, this is the first mixed methods study exploring postoperative neurocognitive recovery after orthopedic surgery.
- Patients own experience of early postoperative neurocognitive recovery has not been reported earlier.
- This study includes a small sample of patients in Sweden and may not be generalizable to other contexts.

Competing interests: None.
Ethical approval: We obtained ethical permit (2019-02968) from the Swedish Ethical Review Authority on 2019-06-19. The study followed the Declaration of Helsinki.
Informed consent: All participants received oral and written information about the study, and written consent was obtained from all participants.
Funding statement: This work was supported by The Research school in Health science, Karolinska Institutet [2020-02641]; and Strategic Research Area Health Care Science, Karolinska Institutet [2-1742/2021].

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1. Introduction

Delayed neurocognitive recovery (dNCR), formerly known as postoperative cognitive dysfunction (POCD) [1] commonly affects older adults within a month post-surgery [2,3] Neuroinflammation and oxidative stress has been demonstrated to be part of the mechanism of dNCR [4,5], and proinflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha enter the brain via normal or disrupted blood-brain-barrier [6]. Yet, at present there are no specific inflammatory biomarkers clinically validated for predicting or diagnosing dNCR [5]. Moreover, fluctuations in tryptophan plasma levels have been suggested as a potential cause of postoperative fatigue, affecting serotonin 5-HT production and contributing to postoperative fatigue through 5-HT-synthesis resulting from changes in plasma amino acid levels [7].

The recovery process from surgery is a multifaceted construct influenced by physical, psychological, and social factors [8]. Patients may regain their preoperative state or surpass it, reaching a high level of well-being and recovering lost functions[8,9]. While perioperative research has emphasized the overall recovery, the understanding of neurocognitive recovery in particular—what it entails, how it is experienced, and its implications—remains ambiguous.

Delayed neurocognitive recovery manifests with cognitive decline in memory, attention, processing speed, and executive functions [1], and is linked to heightened disability risk [10]. Traditionally, dNCR was assessed only through neurocognitive tests [11] but the updated nomenclature includes subjective cognitive decline (SCD) and daily function changes in the diagnosis [1]. SCD, reported even without cognitive impairment, indicates elevated future cognitive impairment and dementia risk [12]. However, perioperative research has primarily focused on quantitative measures of dNCR in the past decades, resulting in subjective reports being overlooked.

Therefore, this mixed methods study aims to fill the current knowledge gap on neurocognitive recovery by integrating quantitative and qualitative data. By exploring neurocognitive performance, blood-borne biomarkers, quality of recovery and older adult patient experiences, we seek to answer the following research question:

1. How do subjective reports (qualitative data) of neurocognitive recovery converge and diverge to neurocognitive assessments, and blood biomarkers (quantitative data)? (mixed methods)

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2. Methods

Study design and setting

This mixed-methods study, had a convergent parallel design [13], and was conducted at a university hospital in Stockholm, Sweden. The mixed methods design was qualitatively dominant [14], and we integrated both qualitative and quantitative approaches [14] with the intention to provide an overview of postoperative neurocognitive recovery, following the Diagnostic and Statistical Manual of Mental disorders fifth edition (DSM-5) criteria for mild/major neurocognitive disorders [15] . We collected and analyzed the quantitative and qualitative data separately, subsequently merged to identify any convergences, divergences, or relationships between the two.

We obtained ethical permit (2019-02968) from the Swedish Ethical Review Authority on 2019-06-19, registered the study at ClinicalTrials.gov (NCT05361460), and published the study protocol [16]. We recruited patients at the scheduled clinical preoperative visit, provided study information, and obtained written informed consent from all patients, following the Declaration of Helsinki [17].

Study population

Between October 2019 and November 2021, we included 46 patients aged ≥60 years scheduled for total hip arthroplasty, dropouts were 6 patients (Figure 1). The recruitment was extended 1,5 years due to COVID-19 outbreak. All underwent both the quantitative and qualitative data collection. Exclusion criteria were: Mini Mental State Examination (MMSE)[18] ≤22, nervous system disease, dependence on antidepressant or tranquilizer, alcohol or drug misuse, hearing or visual impairment, surgery in the previous 6 months, and non-Swedish fluency.

Procedure

The preoperative assessment at the orthopedic clinic included a neurocognitive test battery (ISPOCD), blood sampling, and assessment with Swedish quality of recovery (SwQoR). The postoperative assessment on days 1 to 3 included blood sampling and SwQoR. On day 13 to 16, the postoperative assessment at the orthopedic clinic included the test battery, blood sampling, SwQoR, and semi-structured qualitative interviews. This timeline was selected to capture delayed neurocognitive recovery, which is manifested within 30 days after surgery [19].

Outcome measures

We obtained demographic and perioperative data from patient records, including comorbidities, age, sex, MMSE score, pain intensity with numeric rating scale (NRS), education level, cohabitant status, American Society of Anesthesiologists classification (ASA-classification), anesthetic technique and duration, and duration of the surgery.

Neurocognitive assessment

We measured neurocognitive performance with the International study of postoperative cognitive dysfunction (ISPOCD) test battery [20], administered by the fourth author, trained in neurocognitive testing. The battery includes four neurocognitive tests [20]

1. **Visual Verbal Learning Test (VVLT)** measuring verbal episodic memory, based on Rey's auditive recall of words[20], includes 15 words in 3 trials. A higher total word count indicates better scores.
2. **Concept Shifting Test (CST)**, measuring visual mental flexibility, based on the Trail Making Test[20] includes 16 circles in 3 trials. Less time and fewer errors indicate better scores.
3. **Letter-Digit Coding Test (LDC)**, measuring executive attention, working memory and speed, based on the Symbol Digits Substitution Test[20] during 60 seconds. High scores indicate better performance.
4. **Stroop Colour-Word Test (SCW)**, measuring executive selective attention [20], includes 40 words in 3 trials. Less time and fewer errors indicate better scoring.

Patient reported quality of recovery

We assessed postoperative quality of recovery with the 24-item Swedish quality of recovery (SwQoR) questionnaire. Each item measures various symptoms or discomfort related to surgery and anesthesia such as pain, nausea, anxiety, sleep difficulties, fatigue. The patient rates these items on an 11-item scale, ranging from 0 (indicating none of the time) to 10 (indicating all the time). The range of SwQoR is from 0, indicating excellent quality of postoperative recovery, to 240, indicating poor quality of postoperative recovery. The patient is considered to have a good postoperative recovery if they have a global score less than 21 on postoperative day 14. The SwQoR has been validated in a Swedish setting with postoperative patients [21,22].

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Blood-borne biomarkers

We measured inflammatory biomarkers Granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-ɣ), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), (IL-8), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α), and the non-inflammatory biomarker Tryptophan at the preoperative visit, postoperative day 1 and on day 13-16 to assess its association with neurocognitive recovery. We took peripheral blood (11 mL whole blood) from the patient, centrifuged it, and plasma was stored at -80 degrees Celsius until analysis. Tryptophan was measured using the standardized technique High Performance Liquid Chromatography (HPLC). We analyzed all blood samples in August 2023, with the BIO-RAD Bio-Plex Pro Human Cytokine 8-plex Assay #M50000007A.

Qualitative data

Face-to-face interviews were conducted two weeks after surgery, questions covering cognitive functions, daily activities, and overall mood using an interview guide (Supplementary material 2). Each interview was audio-recorded, and transcribed verbatim.

2.4 Data analysis

Quantitative analysis

We calculated means, SD and median score or time for each sub-test in the ISPOCD, and means, SD for SwQoR. Cognitive performance changes were adjusted for practice effects and variability using age-matched nonsurgical controls. Z-scores were calculated to assess changes from preoperative to postoperative tests with dNCR defined as a z-score of ≥1.0 on day 13-16 after surgery, z-score of <1.0 on day 13-16 indicated no decline according to the ISPOCD [20] We followed the diagnostic rule for, meaning decline in at least two sub-tests [11]. We used IBM SPSS version 28 (IBM Corp., Armonk NY) for statistical analysis.

2.5 Qualitative analysis

Four authors (AA, GM, JE, LB) analyzed the qualitative data. We applied Elo & Kyngäs [23] description of content analysis to the data, with a deductive and inductive approach. We initially chose a set of categories i.e., cognitive domains; attention and memory and, executive functions based on theoretical framework [24], and our research objectives. These categories served as a structured matrix to code the data. As our analysis advanced, we recognized a recurring affective theme in the interviews. We openly coded these meaning units and categorized them as psychological factors, aligning with our research questions and

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acknowledging their influence on neurocognitive recovery. The analysis process involved several iterative steps. First, we read the verbatim transcribed interviews thoroughly. Then, we developed a structured categorization matrix (Supplementary Material 1), and reviewed and coded the data according to the categories and subcategories, and only extracted data that fit the final matrix [23]. Lastly, we held meetings regularly within our research group to achieve agreement on the data analysis.

2.6 Mixed methods analysis

First, we analyzed the qualitative and quantitative (neurocognitive test results) datasets separately, then we merged the results from the datasets by conducting a thorough side-by-side comparison, visualized in the joint display (Table 3) [25]. This comparison enabled us to assess for confirmation, discordance, and expansion of the datasets, and draw meta-inferences [25].

Patient and public involvement

Patients and public were not involved in the design, conduct, reporting or dissemination of this research.

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3. Results

This section starts with patient characteristics based on assessment data including biomarkers, followed by domain-level findings on executive functions, attention and memory, and psychological factors. In the Discussion section, the integrated results are further expanded through a joint display (Table 3).

Patient characteristics and perioperative data

Patient characteristics and test results on a group level are presented in Table 1 and 2. Most patients (n=36) received spinal anesthesia, either with 0.25 ml morphine (0.4 mg ml) and 2.8 ml bupivacaine (5 mg ml) at level L3–L4 or L2-L3, or with 3.5 ml bupivacaine (5 mg ml) only. Four patients underwent general anesthesia with tracheal intubation, using a combination of induction drugs such as Alfentanil, Propofol, Fentanyl and a variation of neuromuscular blocking drugs, and maintenance anesthesia with Sevoflurane.

Neurocognitive assessment

Among the 40 patients, five were classified as dNCR (z-score >1.0 in at least two sub-tests), with no statistical differences in anesthetic factors or characteristics between those with/without dNCR. The mean scores for each sub-test is presented in Table 2.

Patient reported quality of recovery

On postoperative day 14, the patients' postoperative recovery global score was mean 40.9 (Table 1) indicating low quality of recovery. There were no differences in SwQoR scores between those with/without dNCR.

Blood borne biomarkers

One patient did not have a preoperative inflammatory biomarker result, and three patients had missing results on the first postoperative day. The cytokines GM-CSF, IFN-γ, IL-10, IL-2, and IL-4 were undetectable in all patients, while IL-6, IL-8, TNF-α were detectable but below 0 pg/mL. Tryptophan levels (Table 1) were low both preoperatively and postoperatively in the total sample.

Executive Functions

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Among the participants, n=12/40 declined on the Stroop Color Word test, n=10/40 on the Concept Shifting Task test, and n=8/40 on the Letter Digit Coding test (Table 3). Moreover, in the interviews (Supplementary material 1), the most significant and frequent problems the patients described was related to their executive functions. The main qualitative findings were associated to *Problem-solving, Emotional regulation, Energization and Fatigue.*

These challenges manifested considerably when patients tried to resume their everyday activities at home or work, including meal preparation and initiating social contacts. While some patients dedicated effort to their physical rehabilitation, others refrained due to energy constraints, recounting days spent entirely in bed.

The patients described developing new strategies and skills to deal with the current changed form, where some patients learned to carry the mug in another way, using a basket to carry the plate with food to the bed to eat, using a ladder with help from spouse or if the patient was living alone, this also affected their strategy, doing the task independently:

> And I have learned to walk, so that it works. But it was an effort I didn't think I would have to make. But it was the first time in these 50 years that I feel strained (P01).

The effort to sustain energy to certain activities became particularly apparent in patients living with spouses or children, as these family members assumed every task, from dressing to household chores. Patients struggling with these limitations often experienced emotional turmoil, expressing anger, impatience, and frustration upon realizing their changed capacity for simple everyday tasks:

> I've been a bit grumpy, I guess. I don't need to hide that. But no one has taken offense. I've tried to be kind and nice, but sometimes you just snap a bit (P10).

These issues with regulating emotions were previously unfamiliar to the patients and sometimes led to strained relationships, as some patients vented their emotions on their spouses.

The patients' coping mechanisms varied, with some patients testing how far they could go in attempting pre-surgery activities such as leaving the house and go on a walk. Conversely, others embraced their current limitations, recognizing the futility of certain tasks during this phase of recovery. The patients conveyed a profound sense of fatigue or lethargy, irrespective

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of what they did or following specific activities. This fatigue was articulated on either cognitive and motoric domain, or both:

> The only thing I've managed is to go to the bathroom and take care of my needs and... yes, brush my teeth and things like that. // I can handle such tasks, but nothing else. I don't have the energy for it, I'm too tired. // I couldn't even dress myself at first. My husband had to help me get dressed, you know (P06).

In response to this fatigue, patients adopted alternative coping mechanisms. Some patients resorted to daytime sleeping while others avoided activities. This avoidance, distinct from their pre-surgical behaviour, was characterized by patients refraining from planned activities. For instance, they reported a shift from an intention to tidy up the house to do nothing at all. Similarly, they described avoiding interactions with friends or family members due to a lack of energy to engage in conversations.

Attention and Memory

In the Visual Verbal Learning test, n=4/40 patients declined. The main qualitative findings were related to *Subjective or Family concerns of Memory decline, Sustained attention, and Mind wandering.*

Patients frequently described instances of forgetfulness, such as entering the kitchen or bathroom and subsequently forgetting their intended tasks. Some explicitly acknowledged memory decline, recognizing pre-existing issues even before surgery. Patients who experienced forgetfulness occasionally questioned themselves, speculating whether such lapses existed before surgery.

> Yes, I feel like I've had a really poor memory for a long time now. Because I've been anxious about the surgery, and that affects concentration a bit. And I haven't been feeling very well before either (P07).

Others recognized their memory decline to aging. For example, one patient expressed family concern, revealing that a family member had commented on his memory loss recently. As a result, the family member had taken over tasks the patient once handled independently. Consequently, the patient articulated he perceived a memory loss.

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Some patients described how their minds wandered, especially during activities like reading, or showering leading to difficulties in sustaining their attention. As a result, they often abandoned the task. In contrast, others created adaptive strategies to manage their focus and memory, such as pre-planning their medication routine and organizing pills in specific containers.

Psychological factors

The main qualitative findings were related to *Sense of agency, powerlessness, physical limitations, and future perspectives.*

In the interviews, some patients expressed a sense of relief and improved well-being post-surgery, assigning it to the resolution of long-term pain that had accompanied every movement before surgery. This positive change had a notable impact on their mood, as they reflected on their pre-surgery state characterized by persistent pain.

> I feel much more positive now than right after the surgery, as I sense that the pain is heading in the right direction, and the mobility in the operated leg also feels much better, in that way. So, I feel that I am regaining a bit more zest for life compared to before the surgery (P03).

On the contrary, other patients conveyed feelings of powerlessness and dependence on family members post-surgery, particularly in managing daily activities. Despite their family members' well-intentioned efforts to protect them, this gave rise to annoyance. The patients had a desire to maintain a sense of agency even though their abilities had changed post-surgery. This transition from independent functioning to reliance on others resulted in feelings of despair or a bad mood:

> …To 110%. I don't want to be dependent…Yes, I become disheartened and a little angry, and... What should I say?... Just this being dependent, it's... Yes, I want to do everything myself if I may say so. Control my day, or control and manage and so on (P08)

Expectations for the future and the ability to function independently raised concerns, especially regarding the possibility of driving a car again. These worries about the future, coupled with doubts about improvement, led to mood disturbances such as irritability and feeling low.

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> I have a different way, a different temperament. I don't recognize myself. I am sometimes sad, and that's not something I used to be (P46).

Several patients spoke about the significant shift from being in control pre-surgery to a postoperative state where they felt a loss of control over their bodies, their capabilities, and a sense of being different. This perceived loss of control within the healthcare system left patients feeling exposed.

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4. Discussion

We explored how 40 older adult patients experienced neurocognitive recovery after total hip arthroplasty and how this experience aligned or differed with neurocognitive assessment and biomarkers. Interestingly, no apparent differences were observed between those with detected dNCR and those without, whether in qualitative or quantitative data collection. Consequently, the data was presented at the group level.

In the neurocognitive tests, only five patients were classified as dNCR. However, more patients showed impairments in individual cognitive domains. This indicates that, although they did not meet the criteria for dNCR, they still experienced some degree of cognitive impact, as presented in the joint display (Table 3). Among patients classified as having dNCR, no specific subjective complaints or expressions of worry were reported during the qualitative interviews. Moreover, subjective cognitive decline was widely expressed by many patients in the interviews. The incongruence between the objective test results and subjective cognitive decline is anticipated [26], as the controlled neurocognitive test environment lacks external distractions compared to home or the workplace. Patients may demonstrate normal cognitive performance briefly during the test, but their day-to-day functioning could be compromised, leading to subjective cognitive decline [27] which became noticeable in the qualitative data. Furthermore, our findings align with previous research that discovered no correlation between cognitive performance and self-reported cognitive complaints [2,27-29]. Nonetheless, subjectively reported data in perioperative research is often obtained with a variability of methods, such as questionnaires [29], phone interviews post-surgery [28,30], or a single-item binary question [2]. The variability in data gathering poses a substantial challenge in consolidating findings and identifying comprehensive patterns. The diverse definitions and measurement approaches for SCD further complicate this task. In contrast, aging research on SCD has primarily focused on symptom type and intensity, with a higher symptom burden increasing the risk of clinical progression [31].

We found no association between inflammatory biomarkers and dNCR, consistent with other studies [32-34]. As the inflammatory biomarkers were either undetectable or below 0 pg/L, they were excluded from the joint display. Previous studies vary in their results when using inflammatory biomarkers to detect dNCR, these variations may be due to different types of surgery and different methods of analysing inflammatory markers. For example, a meta-analysis [32] revealed an association between elevated C-reactive protein levels in both

postoperative delirium and cognitive decline. However, insufficient evidence was available to draw conclusions regarding IL-6, while IL-8, IL-10, and TNF-α showed no significant association with cognitive decline. Similarly, a recent systematic review [35] noted elevated IL-6 levels within <12 hours postoperatively in older adults but found no such association for TNF-α. Another study focusing on older adults after hip fracture surgery, indicated that glucocorticoid administration reduced levels of IL-6 and TNF-α. [36]. Perioperative administration of glucocorticoids, commonly used in orthopaedic surgery, and non-steroidal anti-inflammatory drugs (NSAID), frequently prescribed for osteoarthritis [37], have been found to suppress cytokines including IL-6 and TNF-α [38]. Aligning with these findings, updated European guidelines on postoperative delirium advise against the use of biomarkers for prediction or prevention of delirium in patients at-risk [30]. Nevertheless, it remains uncertain whether this recommendation extends to delayed neurocognitive recovery, posing implications of the design of future trials.

Tryptophan levels were consistently low in our patients, similar to findings in a study of patients with cancer-related fatigue [39]. Interestingly, mean tryptophan levels in other studies were higher: 74.4 µM in patients with cancer-related fatigue [40] and 65 µmol/L in bariatric surgery patients [41]. Besides the serotonin pathway, tryptophan is catabolized in the kynurenine pathway and plays a role in energy homeostasis. Changes in this pathway can be associated with low grade inflammation [40] which is relevant to our patient group with osteoarthritis, a chronic inflammatory condition. Postoperative fatigue, characterized by persistent weakness or tiredness is frequently overlooked, and significantly impacts cognitive, behavioral and physical functions, often delaying the resumptions of daily activities after surgery [42]. We found that two of the most frequently described symptoms in the qualitative data was lack of energy and lethargy impacting the patient's daily functioning after surgery, aligning with previous research [43]. However, we did not ask how their energy levels were before the surgery. Lethargy and lack of energy may be interpreted as fatigue which is not traditionally a component in neurocognitive tests even though it impacts cognitive functioning. Assessment of postoperative fatigue can be a helpful element, in addition to neurocognitive assessments to predict postoperative recovery. Furthermore, each meaning unit from the qualitative data may not exclusively correspond to a singular cognitive domain but can in fact match to more than one, such as subjective complaints about attention could match with memory. Previous literature indicate attention, working memory, and executive control share substantial similarities in their functional and structural neural correlates [44].

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Postoperative pain was well-controlled, as evidenced by the low pain scores. While some patients described an improved sense of well-being after experiencing pain relief following surgery, others expressed concerns about the future and the ability to function independently. The different coping strategies which the patient employed to resume daily activities aligns with earlier studies [43,45,46]. In our study, patients described low mood, dependency on others and perceived loss of agency which impacted their daily functioning due to the surgery. Earlier studies [43,46-48] have found that psychological factors, specifically vulnerability factors like depressive and anxiety symptoms affect postoperative recovery. These factors not only manifest behaviourally through avoidance behaviours but also have cognitive implications [49]. Patients described how social support facilitated a smoother postoperative recovery process. Social support is related to improved global cognitive function, executive functions and memory [50]. In our study, most patients resided with a spouse and received support in their daily activities e.g., help with dressing, and cleaning. On the other hand, some patients expressed a sense of powerlessness due to their reliance on others. For them, depending on external support symbolized discomfort in seeking help. Therefore, clinical implications should include assessing surgical patients for emotional stress, such as depression and anxiety, as these factors are important predictors of postoperative recovery. Behavioural therapeutic interventions can be effective in addressing these concerns [51].

The overall postoperative recovery score was 40.9 on a group level, meaning they had a higher postoperative symptom burden and low quality of recovery, whereas a score <21 on postoperative 14 , would indicate they had a good postoperative recovery [22]. However, the quality of recovery score in the referenced study pertains to a day surgery unit with a mix of young and older patients, which may not be directly applicable to our group consisting of older adults with comorbidities.

To our knowledge, this is the first mixed-methods study exploring delayed neurocognitive recovery together with psychological factors after total hip arthroplasty. All participants underwent qualitative interviews, blood tests, and neurocognitive tests, and our results present detailed descriptions of postoperative neurocognitive and emotional recovery. However, limitations include strict eligibility criteria which led to the exclusion of many patients. This strictness may have excluded frailer individuals, e.g., those with nervous system diseases. Moreover, generalizability of our results is limited due to small number of participants and patient-reported symptoms. Another limitation is the lack of standardized delirium assessment

while patients were at the hospital and preoperative depression screening. However, the SwQoR does include items assessing anxiety and depressive symptoms. While we acknowledge the potential for bias with the same person conducting both tests and interviews, efforts were made to minimize bias by standardizing the test procedure and instructions provided to all participants.

Future direction should involve multidisciplinary teams that bridge specialty, primary, and social care services. Long-term follow-ups should include objective neurocognitive assessments, evaluations of fatigue, and measurements of instrumental daily activities. Additionally, patients' subjective reports must be gathered in accordance with recommended terminology [1].

Conclusion

In conclusion, this study found a disparity between subjective reports of neurocognitive recovery and assessment methods. Although only a few patients were classified as having delayed neurocognitive recovery after undergoing assessment, many described changes in their daily functioning due to cognitive symptoms. The data highlights the complexity and breadth of postoperative neurocognitive symptoms which extend beyond psychometric testing and blood samples. Furthermore, psychological factors such as low mood and a sense of agency was found to be a significant influencer of postoperative recovery.

Authors contribution

Conceptualization: Jeanette Eckerblad, Lina Bergman, Ulrica Nilsson.
Methodology: Anahita Amirpour, Jeanette Eckerblad, Lina Bergman, Ulrica Nilsson.
Formal analysis: Anahita Amirpour, Gabriela Markovic, Jeanette Eckerblad, Lina Bergman, Ulrica Nilsson.
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Funding acquisition: Jeanette Eckerblad, Lina Bergman, Ulrica Nilsson.

Tables and figures

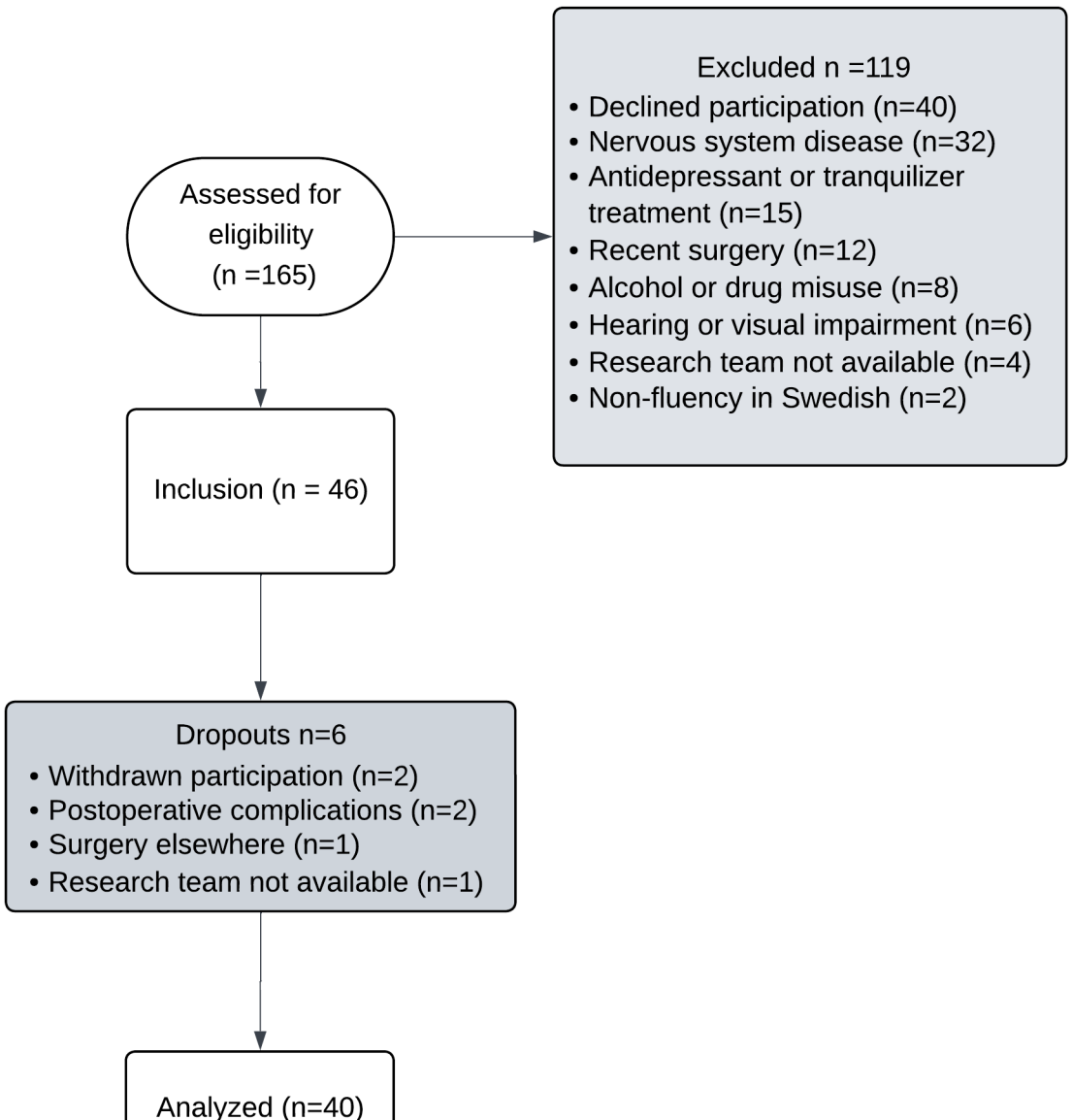

Figure 1. Flow chart of participants.

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Table 1. Patient characteristics.

	Total sample (n=40)
Sex	
Men, n (%)	19 (47.5)
Women, n (%)	21 (52.5)
Age, years	
Mean (min-max)	70 (60-87)
Level of education	
Elementary school, n (%)	11 (27.5)
Upper secondary school, n (%)	13 (32.5)
Tertiary education, n (%)	16 (40)
Living situation	
Lives with spouse or adult children, n (%)	29 (72.5)
Lives with spouse and has home care, n (%)	1 (2.5)
Lives alone, n (%)	9 (22.5)
Lives alone and has home care, n (%)	1 (2.5)
MMSE	
Mean (SD)	28 (1.4)
ASA	
I, n (%)	5 (13)
II, n (%)	18 (45)
III, n (%)	17 (42)
Comorbidities	
Heart disease (e.g., hypertension) n (%)	24 (57)
Vascular disease, n (%)	9 (21)
Lung disease, n (%)	6 (14)
Kidney disease, n (%)	1 (2)
Diabetes, n (%)	5 (12)
History of cancer, n (%)	8 (19)
Autoimmune disease, n (%)	6 (14)
Type of anesthesia	
Spinal, n (%)	36 (90)
General, n (%)	4 (10)
Duration of surgery, minutes (SD)	114.5 (32.4)
Duration of anesthesia, minutes (SD)	188.5 (36.5)
Intraoperative bleeding, ml (SD)	348 (148.9)

Postoperative days at the hospital, (SD)	1.5 (0.6)
Preoperative pain, NRS mean (SD)	5.4 (3.2)
Postoperative pain day 14, NRS mean (SD)	2.1 (2.1)
Preoperative tryptophan µmol/l mean (SD)	43.8 (9.5)
Postoperative tryptophan µmol/l day 13-16 mean (SD)	41.9 (10).
SwQoR global score, day 13-16 mean (SD)	40.9 (28.4)
Postoperative opioid treatment, day 14	
Yes, n (%)	17 (43)
No, n (%)	23 (57)

Abbreviations: MMSE= Mini Mental State Examination; ASA= American Association of anesthesiologists' physical status classification system, NRS=Numeric rating scale, SwQoR=Swedish quality of recovery

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Table 2. Summary of study participants' ISPOCD test results. Mean (SD), Median

	Preoperative (baseline)	Postoperative measurement
VVLT total word count,	22.3 (5.0) Med: 22.0	25.3 (5.9) Med: 25.5
VVLT delayed recall, total word count	8.1 (2.6) Med: 8.0	9.1 (3.2) Med: 9.5
CST, time part C	38.8 (14.8) Med: 33.1	36.9 (13.5) Med: 35.4
CST, number of errors part C	1.5 (2.7) Med: 0	1.1 (2.2) Med: 0
LDC, score	27.5 (5.9) Med: 28	28 (7) Med: 30
SCW, part 3 time	51.4 (19.2) Med: 47.5	50.3 (22.1) Med: 43,8
SCW, number of errors	0,6 (1) Med: 0	0,9 (1,9) Med: 0

Abbreviations: ISPOCD=international study of postoperative dysfunction; VVLT=visual verbal learning test; CST=concept shifting task; LDC=letter digit coding test; SCQ=stroop color word test

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Table 3. Joint display presenting quantitative, qualitative and mixed-methods meta-inferences of domains.

MM domains	**Quantitative findings** **Number of patients with** z-score ≥1.0 i.e., delayed neurocognitive recovery on neurocognitive tests.	**Qualitative findings** **Codes and quotes**	**Meta-inferences**
Executive functions	Stroop Color Word Test (SCW), n=12/40 Concept Shifting Task (CST), n=10/40 Letter Digit Coding Test (LDC), n=8/40	*Performance awareness* So, you learn a lot of tricks, you stand in a corner, brace yourself against your back and stand on the leg you can put weight on. Yeah, then you can play around with the coffee maker (P43). *Having a short fuse* So, I have a pretty short fuse, and I lose patience when things don't go smoothly... like when I can't put on my pants and stuff, so then I get angry. And then it might happen that a crutch ends up in the wall or something (P31)	In the objective test results, only a small number of patients declined on CST, LDC, and SCW. Fatigue was not addressed in the neurocognitive tests, however tryptophan levels were overall low in the total sample. Moreover, the qualitative data brought to light significant changes in patients' daily functioning, including changes in their performance at home or at work. Patients described new challenges in emotional regulation, where they would become frustrated or have anger outbursts on their family members. Some patients described a fatigue-like state, leading them to spend entire days in bed.

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		Not thorough as before and delaying action I notice that's not like me. I am very thorough about everything. But now, there are things everywhere, and, by the way, it's hard to pick up. But I think, well, I'll do that later. But I haven't done it yet (P08). *Motoric fatigue* I am tired, physically ... if I go out and walk, as I have tried to do for the last three days…then I am quite tired afterwards…Yes, it's time to lie down. And then I'm not really fit for fight ... I'm don't have much energy for the rest of the day. (P31)	
Attention **Memory**	Visual Verbal learning test (VVLT), n=4/40	*Doubting memory function* But, you know, it's just that you start to think that you're not sure when you yourself stop noticing that you forget things (P05). *Family member pointing out memory decline* If I have experienced some memory loss, it's possible, it's possible. Because our children said, 'Dad, you won't remember this. It was like this' (P01). *Feeling absent-minded* So right now, I can read and read and read, and still, I find myself stuck on the same sentence, and then	The VVLT evaluates episodic memory at a specific point in time and demonstrated the lowest number of patients declining. The qualitative data showed that patients described attentional changes over time, with only a few acknowledging subjective memory decline or expressing family concerns about memory decline. Feelings of absent-mindedness and a lack of focus were identified as factors influencing both their memory and decision-making regarding the activities they chose to engage in or avoid.

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		and then it's just as good to leave it// Uhm, concentration, I can't concentrate properly (P10).	
Psychologi cal factors		*Wanting to manage things independently* Sometimes it's my dear wife... I become more easily irritated, perhaps. It has to do with her trying to be overly protective and fetch everything for me, and I think to myself, "I can handle this on my own," and then I get slightly annoyed at trivial things that are not relevant (P03) *Being in a bad mood and dependant on others* And the thing about being dependent on other people and... you don't want to bother people, even if they're your own sons, it feels like 'God, how annoying I am.' And then I get in a bad mood (P19). *Feeling low* I feel a bit depressed because I can't do anything, and not fix anything, not fetch anything, not pick up anything (P08) *Brighter outlook* I think maybe I was grumpier before the surgery than after, because now it's done. And now, well, theoretically at least, it can't get worse. Now it's just going to get better (P12)	While objective neurocognitive tests focus solely on cognitive functions, they fall short in capturing the affective component. The qualitative data psychological factors was expanded upon, with patients articulating the impact of factors such as the sense of agency, feelings of powerlessness stemming from dependence on others, and adjustments to new physical limitations. These factors not only shaped their overall well-being but also significantly influenced their relationships and daily functioning. Conversely, a few patients shared a more optimistic perspective on life, attributing it mainly to the relief from previous pain.

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Supplementary material

1. Procedure of content analysis

Categories	Subcategories	Codes	Quotes
Executive Functions	Problem-solving	Performance awareness	And I have learned to walk, so that it works. But it was an effort I didn't think I would have to make. But it was the first time in these 5 years that I feel strained (P01)
			So you learn a lot of tricks. You position yourself in a corner. Leverage against the back, and then you stand on the leg you're allowed to put weight on. Yes, and then you manage some things with the coffee maker (P43)
	Emotional regulation	Feeling grumpy and snapping	I've been a bit grumpy, I guess. I don't need to hide that. But no one has taken offense. I've tried to be kind and nice, but sometimes you just snap a bit (P10).
		Having a short fuse	So, I have a pretty short fuse, and I lose patience when things don't go smoothly... like when I can't put on my pants and stuff, so then I get angry.

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		And then it might happen that a crutch ends up in the wall or something (P31)
Energization	Avoiding initiatives and others	Yeah, I've mostly been lying in bed. That's what I've done and I've been served food and everything, I haven't had to do anything. I have my grandchildren living with me, so he has helped a lot (P06)
	Not thorough as before and delaying action	I notice that's not liking me. I am very thorough about everything. But now, there are things everywhere, and, by the way, it's hard to pick up. But I think, well, I'll do that later. But I haven't done it yet (P08)
Fatigue	Mental fatigue	But administrative tasks are no problem, but sitting down to write assignments, I don't have the concentration for that. I get too tired (P31).
	Motoric fatigue	

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			The only thing I've managed is to go to the bathroom and take care of my needs and... yes, brush my teeth and things like that. // I can handle such tasks, but nothing else, I don't have the energy for it, I'm totally tired. // I couldn't even dress myself at first. My husband had to help me get dressed, you know (P06). I am tired, physically, if I go out and walk, as I have tried more for the last three days…then I am quite tired afterwards…Yes, it's time to lie down. And then I'm not really fit for fight ... I'm don't have much energy for the rest of the day. (P31)
Attention and memory	Subjective memory decline	Doubting memory function	But, you know, it's just that you start to think that you're not sure when you yourself stop noticing that you forget things (P05).
		Memory decline	Yes, I feel like I've had a really poor memory for a long time now. Because I've been anxious about the surgery, and that affects concentration a bit. And I haven't been feeling very well before either (P07).

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Family concern of memory decline	Family member pointing out memory decline	If I have experienced some memory loss, it's possible, it's possible. Because our children said, 'Dad, you won't remember this, it was like this' (P01).
Sustained attention	Losing the thread	Now it can be distracting around as well, I mean you can... what should I say? You lose the thread. If we have a study that we have read, a large section, so... //Now I haven't had the energy to participate and haven't had the energy to read up. I can't go through everything now, no. I don't do that (P06).
	Feeling absent-minded	So right now, I can read and read and read, and still, I find myself stuck on the same sentence, and then and then it's just as good to leave it// Uhm, concentration, I can't concentrate properly (P10).
		Today, I showered with the hearing aids on. It wasn't good (P01).

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		Lack of focus	These last few days, I have found it challenging. I have these magazines that I subscribe to, that I receive. So I haven't had the energy to read them properly. I haven't been able to focus on it (P39).
Psychological factors	Sense of agency	Lack of agency	But it's connected to the fact that I'm the kind of person who has a need for control, too, so that... And you don't have that when you surrender yourself to healthcare. (P05)
		Wanting to manage things independently	Sometimes it's my dear wife... I become more easily irritated, perhaps. It has to do with her trying to be overly protective and fetch everything for me, and I think to myself, "I can handle this on my own," and then I get slightly annoyed at trivial things that are not relevant (P03)
	Powerlessness	Being dependant on others	…To 110%. I don't want to be dependent. Absolutely. … Yes, I

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		become disheartened and a little angry, and... What should I say? //... Just this being dependent, it's... Yes, I want to do everything myself if I may say so. Control my daily or control and manage and so on (P14).
		And the thing about being dependent on other people and... I don't want to bother people, even if they're your own sons, it feels like God, how annoying I am.' And then I get in a bad mood (P19).
Physical limitations	Feeling low	I feel a bit depressed because I can't do anything, and not fix anything, not fetch anything, not pick up anything (P08)
		I have a different way, a different temperament. I don't recognize myself. I am sometimes sad, and that's not something I used to be (P46).

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Future perspectives	Brighter outlook	I feel much more positive now than right after the surgery, as I sense that the pain is heading in the right direction, and the mobility in the operated leg also feels much better, in that way. So, I feel that I am regaining a bit more zest for life compared to before the surgery (P2).
		I think maybe I was happier before the surgery than after, because now it's done. And now, well, theoretically at least, it can't get worse. Now it's just going to get better (P12).

2. Interview guide

Open question to patients, encouraging them to speak freely about their experiences regarding memory, concentration, and recovery after hip replacement surgery.

- How do you perceive yourself from the time you were cared for in the recovery ward until now?
- How would you describe yourself since you underwent your hip replacement surgery?
- Do you recognize yourself after your hip replacement surgery? In what way? Please describe what you mean.
- How is your memory after the surgery compared to before? When and how did you notice any changes? Can you provide an example?
- Do you experience any changes in your concentration and attention? Can you elaborate on what you mean? Would you like to give an example or describe a situation?
- Have you experienced or do you experience changes in your mood after the surgery? Feel free to elaborate on your answer.
- Can you describe your sleep before and after the surgery? If it has changed, what do you think it might be due to? In what way is your sleep changed?
- Do you feel completely restored to your usual self, regarding your cognitive abilities after your surgery? If not, describe freely in what way and how. Can you describe the process?
- How do you perceive your ability to initiate your daily activities? Can you provide examples and describe it?
- How are your energy levels?

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References

1. Evered L, Silbert B, Knopman DS, et al. Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery-2018. *Anesthesiology* 2018; **129:** 872-9.
2. Deiner S, Liu X, Lin HM, et al. Subjective cognitive complaints in patients undergoing major non-cardiac surgery: a prospective single centre cohort trial. *Br J Anaesth* 2019; **122:** 742-50.
3. Evered L, Atkins K, Silbert B, Scott DA. Acute peri-operative neurocognitive disorders: a narrative review. *Anaesthesia* 2022; **77 Suppl 1:** 34-42.
4. Safavynia SA, Goldstein PA. The Role of Neuroinflammation in Postoperative Cognitive Dysfunction: Moving from Hypothesis to Treatment. *Front Psychiatry* 2018; **9:** 752.
5. Evered LA, Silbert BS. Postoperative Cognitive Dysfunction and Noncardiac Surgery. *Anesthesia & Analgesia* 2018; **127:** 496-505.
6. Li Z, Zhu Y, Kang Y, Qin S, Chai J. Neuroinflammation as the Underlying Mechanism of Postoperative Cognitive Dysfunction and Therapeutic Strategies. *Front Cell Neurosci* 2022; **16:** 843069.
7. McGuire J, Ross GL, Price H, Mortensen N, Evans J, Castell LM. Biochemical markers for post-operative fatigue after major surgery. *Brain Research Bulletin* 2003; **60:** 125-30.
8. Nilsson U, Jaensson M, Hugelius K, Arakelian E, Dahlberg K. A journey to a new stable state-further development of the postoperative recovery concept from day surgical perspective: a qualitative study. *Bmj Open* 2020; **10:** e037755.
9. Royse CF. The patient's surgical journey and consequences of poor recovery. *Best Practice & Research-Clinical Anaesthesiology* 2018; **32:** 253-8.
10. Deiner S, Liu X, Lin H-M, et al. Does postoperative cognitive decline result in new disability after surgery? *Annals of Surgery* 2021; **274:** e1108-e14.
11. Borchers F, Spies CD, Feinkohl I, et al. Methodology of measuring postoperative cognitive dysfunction: a systematic review. *Br J Anaesth* 2021; **126:** 1119-27.
12. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol* 2020; **19:** 271-8.
13. Curry LA, Krumholz HM, O'Cathain A, Plano Clark VL, Cherlin E, Bradley EH. Mixed methods in biomedical and health services research. *Circ Cardiovasc Qual Outcomes* 2013; **6:** 119-23.
14. Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. *Kolner Z Soz Sozpsychol* 2017; **69:** 107-31.
15. APA. *Diagnostic and statistical manual of mental disorders: DSM-5*, 5th edn. Washington, D.C: American Psychiatric Publishing, 2013.
16. Nilsson U, Liander K, Rooyackers O, Eriksson LI. Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study. *Bmj Open* 2019; **9:** 6.
17. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013; **310:** 2191-4.
18. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12:** 189-98.
19. Evered L, Silbert B, Scott DA, Eckenhoff RG. Recommendations for a new perioperative cognitive impairment nomenclature. *Alzheimer's & Dementia* 2019; **15:** 1115-6.

20. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998; **351:** 857-61.
21. Jaensson M, Dahlberg K, Eriksson M, Nilsson U. Evaluation of postoperative recovery in day surgery patients using a mobile phone application: a multicentre randomized trial. *Br J Anaesth* 2017; **119:** 1030-8.
22. Nilsson U, Dahlberg K, Jaensson M. The Swedish Web Version of the Quality of Recovery Scale Adapted for Use in a Mobile App: Prospective Psychometric Evaluation Study. *JMIR Mhealth Uhealth* 2017; **5:** e188.
23. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008; **62:** 107-15.
24. Lezak MD, Howieson DB, Bigler ED, Tranel D. *Neuropsychological Assessment*: OUP USA, 2012.
25. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Services Research* 2013; **48:** 2134-56.
26. Wu LM, Tanenbaum ML, Dijkers MP, et al. Cognitive and neurobehavioral symptoms in patients with non-metastatic prostate cancer treated with androgen deprivation therapy or observation: A mixed methods study. *Soc Sci Med* 2016; **156:** 80-9.
27. Dijkstra JB, Jolles J. Postoperative cognitive dysfunction versus complaints: a discrepancy in long-term findings. *Neuropsychology Review* 2002; **12:** 1-14.
28. Dijkstra JB, Houx PJ, Jolles J. Cognition after major surgery in the elderly: test performance and complaints. *British Journal of Anaesthesia* 1999; **82:** 867-74.
29. Moller JT, Svennild I, Johannessen NW, et al. Perioperative monitoring with pulse oximetry and late postoperative cognitive dysfunction. *Br J Anaesth* 1993; **71:** 340-7.
30. Makkar M, Hunter R, Kulkarni A, Nguyen JMV. Postoperative Cognitive Decline in Patients Undergoing Major Gynecologic Oncology Surgery: A Pilot Prospective Study. *J Obstet Gynaecol Can* 2024; **46:** 102584.
31. Earl Robertson F, Jacova C. A Systematic Review of Subjective Cognitive Characteristics Predictive of Longitudinal Outcomes in Older Adults. *Gerontologist* 2023; **63:** 700-16.
32. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *Plos One* 2018; **13:** e0195659.
33. De Cosmo G, Sessa F, Fiorini F, Congedo E. Effect of remifentanil and fentanyl on postoperative cognitive function and cytokines level in elderly patients undergoing major abdominal surgery. *J Clin Anesth* 2016; **35:** 40-6.
34. Fu C, Lin J, Gong G, Zhong W, Chen H, Luo X. Inflammatory markers in postoperative cognitive dysfunction for patients undergoing total hip arthroplasty: a meta-analysis. *Aging-Clinical & Experimental Research* 2022; **34:** 277-88.
35. Patel A, Zhang M, Liao G, et al. A Systematic Review and Meta-analysis Examining the Impact of Age on Perioperative Inflammatory Biomarkers. *Anesth Analg* 2022; **134:** 751-64.
36. Clemmesen CG, Tavenier J, Andersen O, Palm H, Foss NB. Methylprednisolone and inflammatory stress response in older people undergoing surgery for hip fracture: a secondary analysis of a randomized controlled trial. *Eur Geriatr Med* 2019; **10:** 913-21.

37. Ryan PM, Scherry H, Pierson R, Wilson CD, Probe RA. NSAID use in orthopedic surgery: A review of current evidence and clinical practice guidelines. *J Orthop Res* 2024; **42:** 707-16.
38. Yan Y, Guo TM, Zhu C. Effects of nonsteroidal anti-inflammatory drugs on serum proinflammatory cytokines in the treatment of ankylosing spondylitis. *Biochemistry and Cell Biology* 2018; **96:** 450-6.
39. Okinaka Y, Kageyama S, Goto T, et al. Metabolomic profiling of cancer-related fatigue involved in cachexia and chemotherapy. *Sci Rep* 2024; **14:** 8329.
40. Fosså A, Smeland KH, Fluge Ø, et al. Metabolic analysis of amino acids and vitamin B6 pathways in lymphoma survivors with cancer related chronic fatigue. *Plos One* 2020; **15:** e0227384.
41. Christensen MHE, Fadnes DJ, Røst TH, et al. Inflammatory markers, the tryptophan-kynurenine pathway, and vitamin B status after bariatric surgery. *Plos One* 2018; **13:** e0192169.
42. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of postoperative fatigue. *J Psychosom Res* 2004; **57:** 317-26.
43. Cohen CL, Atkins KJ, Evered LA, Silbert BS, Scott DA. Examining Subjective Psychological Experiences of Postoperative Delirium in Older Cardiac Surgery Patients. *Anesthesia & Analgesia* 2022; **06:** 06.
44. Toba MN, Malkinson TS, Howells H, Mackie MA, Spagna A. Same, Same but Different? A Multi-Method Review of the Processes Underlying Executive Control. *Neuropsychol Rev* 2023.
45. Karlsson Å, Olofsson B, Stenvall M, Lindelöf N. Older adults' perspectives on rehabilitation and recovery one year after a hip fracture - a qualitative study. *BMC Geriatr* 2022; **22:** 423.
46. Li L, Dohan D, Smith AK, Whitlock EL. 'It was a great brain, and I miss it': lay perspectives on postoperative cognitive dysfunction. *Br J Anaesth* 2023; **130:** 567-72.
47. Nilsson U, Dahlberg K, Jaensson M. Low Preoperative Mental and Physical Health is Associated with Poorer Postoperative Recovery in Patients Undergoing Day Surgery: A Secondary Analysis from a Randomized Controlled Study. *World J Surg* 2019; **43:** 1949-56.
48. Jaensson M, Dahlberg K, Nilsson U. Factors influencing day surgery patients' quality of postoperative recovery and satisfaction with recovery: a narrative review. *Perioper Med (Lond)* 2019; **8:** 3.
49. Ditton E, Johnson S, Hodyl N, et al. Improving Patient Outcomes Following Total Knee Arthroplasty: Identifying Rehabilitation Pathways Based on Modifiable Psychological Risk and Resilience Factors. *Front Psychol* 2020; **11:** 1061.
50. Mogic L, Rutter EC, Tyas SL, Maxwell CJ, O'Connell ME, Oremus M. Functional social support and cognitive function in middle- and older-aged adults: a systematic review of cross-sectional and cohort studies. *Syst Rev* 2023; **12:** 86.
51. Reza T, Grezenko H, Barker C, et al. Emotional Stress and Immune Response in Surgery: A Psychoneuroimmunological Perspective. *Cureus* 2023; **15:** e48727.

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Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study

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To cite: Nilsson U, Liander K, Rooyackers O, *et al*. Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study. *BMJ Open* 2019;**9**:e032650. doi:10.1136/bmjopen-2019-032650

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-032650).

Received 05 July 2019
Revised 21 November 2019
Accepted 22 November 2019

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ABSTRACT

Introduction In the early weeks after surgery, patients may experience cognitive changes and impaired memory and concentration—changes commonly referred to as postoperative cognitive decline. It is often the patient and/or a relative that initially detects a change in cognitive capacity after surgery, typically when resuming daily activities. We lack information about how patients experience early postoperative cognition (*delayed neurocognitive recovery*) and if these experiences can be reflected in biochemical pattern of inflammatory signalling molecules, cognitive function as well as on quality of postoperative recovery.

Methods and analysis The study has a mixed-methods design that is integration of qualitative and quantitative data within a single investigation. Participants included will be patients aged ≥60 years that are undergoing major elective joint replacement surgery (n=40) and their relative. Patient's experience of his/her early cognition will be captured by interviews on postoperative day 13–16 during the follow-up visit. A relative will also be interviewed on the same day or the day after. Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction test battery. Symptoms/discomfort will be measured preoperatively and postoperatively (on postoperative day 1 and 2 and at the follow-up visit day 13–16) by the Swedish version of Quality of Recovery and by a visual analogue scale assessing pain intensity. Biomarkers will also be collected at the same time points. The findings from the interviews will be sorted out depending on group stratification (no delayed neurocognitive recovery and delayed neurocognitive recovery). The qualitative and quantitative findings will be compared to seek for similarities and differences.

Ethics and dissemination The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments. Results from this study will be disseminated in peer-reviewed journals, scientific conferences and in social media.

Strengths and limitations of this study

- A mixed-methods study comparing patients' experiences of early postoperative cognition with patterns in biochemical pattern of inflammatory signalling molecules, cognitive function assessed with validated neuropsychological tests as well as on quality of postoperative recovery.
- Patients' own experiences of early postoperative cognition including their relative's view have never been reported earlier.
- This study includes a small sample of patients and is conducted in Sweden, and may not be generalisable to other contexts.

INTRODUCTION

Postoperative neurocognitive decline (POCD, previously termed postoperative cognitive dysfunction) is one of the the most common complications after otherwise uneventful surgery and affects multiple cognitive domains such as memory, executive functions, information processing speed and attention[1–5] with subsequently impaired day-to-day memory, language skills, attention and learning compared with levels demonstrated preoperatively.[6] Postoperative cognitive decline is diagnosed up to 30 days postoperatively (*delayed neurocognitive recovery*)[7] and is a subtler deterioration in cognition, as it is not characterised by obvious clinical symptoms such as a change in the level of consciousness.[8] With advanced age as the primary risk factor for neurocognitive decline,[2 4 5 8–10] the incidence of cognitive dysfunction in elderly patients 1 week after surgery is approximately 25%[2 9–11] and remains at 10% at 3 months.[2 9 10] Intraoperative factors have been hypothesised as playing a role in the occurrence of POCD. Yet, choice of anaesthesia (general vs regional) has not been found to influence

development of POCD[8 12 13] as well as the choice of anaesthetic agent,[14] depth of anaesthesia[15] and intraoperative hypotension.[16]

While the mechanism behind postoperative neurocognitive disorders are not fully uncovered, there is a growing body of evidence that surgery-induced inflammation spread systemically via blood-borne immune cells and cytokines to the brain via a disrupted blood-brain barrier, resulting a transient neuroinflammation with impaired cognitive processing.[17 18] It has been reported an inflammatory response to surgical procedure has significant involvement in the POCD development.[11] This postoperative neuroinflammatory reaction can be altered by multiple factors within the perioperative period such as pain, sleep disturbances and prolonged infection.[6]

Because clinical evaluation of the brain is not a routine part of preoperative evaluation[19] and the discrete nature of cognitive disorders, it is often the patient and/or a relative who in the first instance detects a change in cognitive capacity after surgery, typically when resuming daily activities.[5] It has also been reported that elderly patients are 'never the same' after surgery.[12] Evidence suggests that neurocognitive decline can act as a precursor of significant functional impairment following surgery; patients developing neurocognitive decline leave the labour market early and are more dependent on social transfer payments.[20] Neurocognitive disorders are, furthermore, associated with increased mortality[3 20] and with prolonged hospitalisation.[4] Evered *et al* proclaim that perioperative cognition has become largely a research area rather than a clinical state meaning that subjective aspects are rarely sought or reported as well as capacity for activities of daily living is overlooked. Therefore, a subjective report from the patient is an essential element of diagnosing a perioperative neurocognitive decline.[7]

Aim

The aim of present study is therefore to explore patients' experiences of their early postoperative cognition after major orthopaedic surgery in relation to postoperative cognitive function assessed with validated neuropsychological tests, inflammatory signalling molecules and quality of postoperative recovery as well as to describe the relative's view of early postoperative cognition.

METHODS AND ANALYSIS

Study design

A mixed-methods study that is inductive concurrent design where the core component is qualitative and the supplemental component is quantitative with integration of qualitative and quantitative data within a single investigation[21 22] will be undertaken to address the research questions. Study recruitment started in October 2019 and is planned to end in April 2020.

Participants

Patients

Participants included will be patients undergoing major elective joint replacement surgery (n=40) at a university hospital in Sweden. The sample size is based on the mixed-methods study design and the incidence of early cognitive decline at 1–2 weeks postoperatively of 17%–25%.[2 23] However, unpublished research with new reference values indicates that the incidence is underestimated, and instead up to 50% can suffer from POCD.

Exclusion criteria: a score on the Mini-Mental State Examination (MMSE) at screening of ≤22, that is, suspected dementia[24]; <60 years of age; suffering from a nervous system disease; taking tranquillisers or antidepressants; underwent a surgical procedure in the previous 6 months; inability to read and speak Swedish or suffering from a severe visual or auditory disorder, alcoholism or drug dependence.

Relatives

One close relative (spouse or children with age ≥18 years) per patient will be asked to participate. Inclusion criteria for the relatives included identifying themselves as being a relative whom the patient included in the study and being able to take part in an interview in Swedish. The patient decides which relative should be asked. If the relative does not accept to be included, the patient will not be excluded.

Recruitment

One of the researchers will, during their preoperative anaesthesia consultation, provide oral and written information about the study. The details of the study and its potential benefits as well as risks will be explained thoroughly to the patient. If the patient agrees to participation in the study, they will undergo the MMSE screening. Values >22 indicated that the patient is eligible to participate (figure 1).

Qualitative data

Interviews

The patients and their relative will be interviewed separately. The opening question to the patients is: *"How do you yourself experience the time after the operation compared to before?"* Opening question to the relative: *"How would you describe your relative regarding being as they used to be, being themselves, before the operation compared to the time after surgery"*. Probing questions were asked such as *"What do you mean?"* and *"How would you describe that?"* The informants will be encouraged to speak freely about the experience. An interview guide will be used to ensure covering issues such as cognition, memory loss, attention, mood and daily activity.

Quantitative data

Cognitive testing

Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction (ISPOCD)

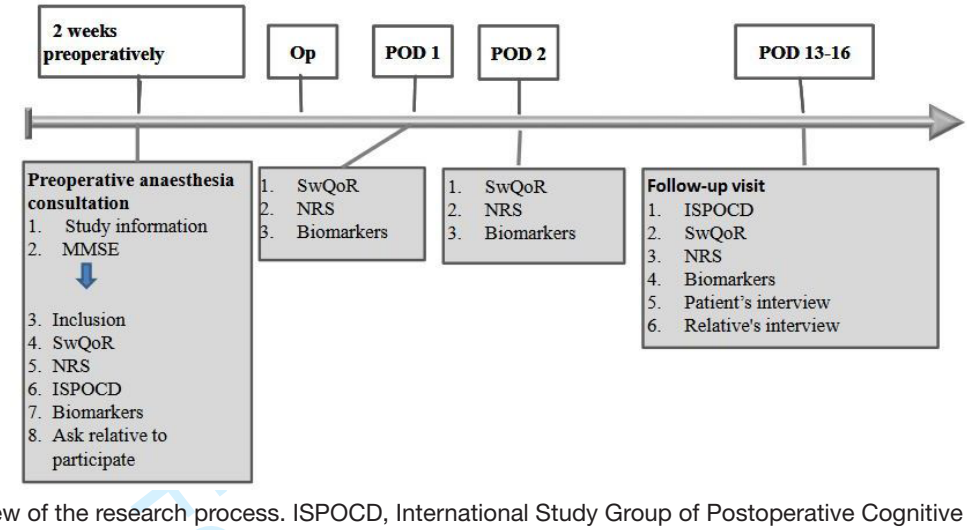

Figure 1 Overview of the research process. ISPOCD, International Study Group of Postoperative Cognitive Dysfunction; MMSE, Mini-Mental State Examination; NRS, numerical rating scale; POD, postoperative day; SwQoR, Swedish version of Quality of Recovery.

neuropsychological test battery. The ISPOCD battery assesses cognitive performance using four different tests, providing seven variables for analysis, including Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Colour-Word Test, the Letter-Digit Coding Test[2] and has been validated in the perioperative setting for two decades.[6] The tests will be administered in the same sequence at each test session by the same researcher following a standardised instruction manual in order to ensure as uniform a test situation as possible. The tests will be carried out in quiet rooms and only the patient and a researcher (KL) will be present.

Blood-borne biomarkers

Inflammatory signalling molecules such as C reactive protein, interleukin 1-beta, interleukin-6, interleukin-10, High Mobility Group Box 1 (HMGB-1) and fractalkine will be measured preoperatively and postoperatively. Venous blood samples (20 mL whole blood) will be drawn from an intravenous cannula. Blood will be centrifuged and plasma stored at −80°C until further analysed.

Quality of recovery

The patients' quality of recovery will be measured by the Swedish version of Quality of Recovery (SwQoR), which measures 24 different items related to symptoms/discomfort that appear postoperatively, such as pain, anxiety, sleep difficulties, dizziness, fatigue, returning to work or usual home activities. The items are rated on 11-point numerical scales ranging from 0, 'none of the time', to 10, 'all of the time'. Reliability and validity tests have provided evidence that it is appropriate to use SwQoR in patients undergoing surgery.[25]

Pain intensity

Pain intensity will be measured using a numerical rating scale (NRS) from 0=no pain to 10=maximum possible pain. The NRS has been tested for reliability and validity in a Swedish population.[26]

Demographic and perioperative data

These include: age, sex, MMSE score, comorbidities, American Society of Anaesthesiologists classification, aesthetic technique and duration, duration of the procedure, blood loss (mL), blood transfusion (mL), use of analgesics during hospitalisation and at home until the follow-up visit, postoperative complications and length of stay.

Procedure

Preoperative data collection

If the patient chooses to participate in the study, they will undergo the cognitive test preoperatively. The test will be performed in an undisturbed room where only the patient and researchers will be present. The tests are expected to take about 20 min. Blood-borne biomarkers will be collected and SwQoR and pain intensity questions will be measured after the cognitive testing is completed (table 1 and figure 1). The day and time of day for preoperative data collection will be documented.

Postoperative data collection

The cognitive test and the interview with the patients will take place on postoperative day 13–16 during the patient's follow-up visit. After the cognitive test is completed, SwQoR and biomarkers will be measured. The patient's relatives will be interviewed separately on the same day or the day after and by the same researcher (KL). All cognitive tests will be performed by one of the researchers from the research group (KL), with education and experience of performing the test. SwQoR, pain intensity and blood-borne biomarkers will be measured postoperative day 1–3, the same time of day ±2 hours and on day 13–16 during patient's follow-up visit. The day and time of day for sampling biomarkers at the follow-up visit will be documented. A research nurse at the Clinical Research Unit at the University Hospital will collect all biomarkers (table 1 and figure 1).

Table 1 Outcome measures

Outcome		Preoperative	POD 1	POD 2	POD 13–16
Cognitive test	ISPOCD battery	X			X
Neuroinflammatory reaction	Blood-borne biomarkers	X	X	X	X
Postoperative recovery	Swedish version of Quality of Recovery questionnaire	X	X	X	X
Pain intensity	Numerical rating scale	X	X	X	X
Experiences of postoperative cognition	Interviews with patients and relatives				X

ISPOCD, the International Study Group of Postoperative Cognitive Dysfunction; POD, postoperative day.

Data analysis

Qualitative data analysis

All interviews will be transcribed verbatim and analysed in line with an inductive thematic analysis.[27] In the first step, all interviews will be read through, patients and relatives separately, and expressions concerning the experienced postoperative cognitive decline will be marked. At the same time, initial reflections on the data will be noted. In the second step, the marked expressions will be coded into a condensed, semantic description of the experiences expressed. Third, themes will be identified, based on sorting the codes and initial reflections. In this step, relations between and levels of the themes will also be mapped. In step four, a review of the themes will be conducted, in which all codes included in a theme are considered, following which the whole analysis is considered in relation to the initial reflections and original texts. Thereafter, all themes and subthemes will be named. The findings from patients and relatives will be presented separately as well as being compared to seek for similarities and differences, and will be highlighted. Also, individual similarities and differences within the couples will be presented. The data analysis will be blinded to the findings from the biomarkers, cognitive tests, SwQoR and pain in order to not be influenced. The analysis will be performed in Swedish and thereafter be translated into English.

Quantitative data analysis

Changes in cognitive performance will be calculated for each of seven test variables and corrected for practice effects and variability using data from a historical age-matched control group that has undergone testing using the same battery and with the same intervals.[2] To quantify the change from preoperative test to the postoperative tests scores, separate and composite z-scores will be calculated on the basis of the seven cognitive test results and compared using Mann-Whitney U rank sum test.

To analyse differences in biomarkers within patients and between patients, χ^2 or Student's t-test will be used. To analyse differences within patients and between patients in cognitive performance and postoperative recovery, Mann-Whitney U rank sum tests will be used. For statistical analyses, IBM SPSS statistics V.24 for Windows will be used (IBM, Armonk, New York, USA). A p value of <0.05 will be considered to be statistically significant in all analyses.

Descriptive statistics of demographic and perioperative data will be presented by number, percentage and mean (SD) or min-max, as appropriate. Depending on the results from the cognitive tests and biomarkers, the patients will be stratified on the basis of their postoperative composite cognitive z-score result into two groups: no delayed neurocognitive recovery corresponding to a composite z-score <1 or delayed neurocognitive recovery with composite z-score ≥1.0.[2] Patient characteristics will be compared, between these two groups, using Fisher's exact test for categorical outcomes and t-tests or the Wilcoxon rank-sum test for continuous variables, as appropriate. A difference will be considered if any of these characteristics between the two groups has a p value of <0.05.

The analytical point of integration

The qualitative and quantitative findings will be brought together to look for similarities, that is, whether the qualitative and the quantitative findings yield convergent results (*triangulation*)[22] or if they are diverged. Thereafter, the findings from the interviews, both patients and relatives, will be sorted out depending on group stratification (no delayed neurocognitive recovery or delayed neurocognitive recovery). The qualitative and quantitative findings will then be compared to seek for similarities and differences. All patients will be included in the mixed data analysis even though they have an improvement in z-score, SwQoR or biomarkers.

Dissemination

The study results will be disseminated through peer-reviewed publications and conference presentations to the scientific community and social media.

Patient and public involvement

Patients were not involved in the design of the study and will not be involved in the recruitment of participants. The results of the project will be disseminated through scientific papers.

DISCUSSION

Knowledge can be obtained both by understanding and explaining a phenomenon of interest, which is the reason why a mixed-methods design including both qualitative and quantitative data will be used. By merging qualitative and quantitative data, we will look for confirmation, expansion and discordance in the different datasets. Confirmation occurs when the data confirm each other, that is, that the results from the qualitative and quantitative analyses confirm the results in the respective outcome. The data can also expand, that is, when the outcomes diverge and expand or complement the results from the qualitative and quantitative findings. Discordance occurs when the results from the different data conflict, or disagree, with each other.[21 22] When results from the quantitative and qualitative study do not match completely, this enhances the robustness of the study by illustrating the complexity of the problem studied.[28] In this study, the quantitative data include both objective (biomarkers and cognitive testing) and subjective (SwQoR and postoperative pain) outcomes and the qualitative data include both the patient's and the relative's view.

POCD is a major neurological adverse outcome following major surgery[5 6 29] with age as one of the major risk factors.[2 4] Cognitive assessment in order to capture POCD is not a routine part of clinical practice, and nor do we have any evidence for patients' and their relatives' own experience of suffering from POCD and whether there is a relation between objective and subjective outcomes of it. The knowledge from the present project as well as earlier evidence from studies assessing POCD will create a base in developing a gamified version of the traditional pen-and-paper cognitive assessment tools, in order to start assessing POCD in an easy and secure way in clinical practice. Until this is done, the results from the present project will generate evidence for clinical practice to detect patients with POCD by identifying signs and symptoms that patients and their relatives themselves describe when suffering from POCD.

ETHICAL CONSIDERATIONS

It is recognised that the study protocol involves cognitive tests that may display pre-existing and previously unknown cognitive impairment.[30] Detailed information about the extent and duration of cognitive tests, including possible outcomes, will be carefully explained and the patient and the relative can refuse to participate on the basis of this information. In addition, participants will be informed that the study is voluntary and that the data would be treated with confidentiality. They will also be informed that they can terminate their participation at any time. Written informed consent will be obtained from the participants after they have received written and verbal information about the study, including the purpose and procedures, the voluntariness of participation and the option to withdraw at any time. They will also be guaranteed confidentiality and secure data storage. We will follow good clinical practice in the conduct of clinical trials.

The study follows the recommendations of the World Medical Association General Assembly that include principles considering the prospective registration and the public disclosure of study results to be ethical obligations, as follows: '*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject*' and '*Negative and inconclusive as well as positive results should be published or otherwise made publicly available*'. All researchers will follow the Uniform Requirements for Manuscripts.[31]

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Contributors UN has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version. KL has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version. OR has contributed to the planning of the biomarkers and the preparation of the manuscript and approved of the final version. LIE has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand* 2010;54:951–6.
2 Moller JT, Cluitmans P, Rasmussen LS, *et al*. Long-Term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *The Lancet* 1998;351:857–61.
3 Monk TG, Weldon BC, Garvan CW, *et al*. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008;108:18–30.
4 Newman MF, Kirchner JL, Phillips-Bute B, *et al*. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001;344:395–402.
5 Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. *Best Pract Res Clin Anaesthesiol* 2006;20:315–30.
6 Funder KS, Steinmetz J, Care C. Post-Operative cognitive dysfunction – lessons from the ISPOCD studies. *Trends in Anaesthesia and Critical Care* 2012;2:94–7.

7 Evered L, Silbert B, Knopman DS, *et al*. Recommendations for the nomenclature of cognitive change associated with anaesthesia and Surgery-2018. *Anesthesiology* 2018;129:872–9.
8 Steinmetz J, Rasmussen LS. Postoperative confusion. *Minerva Anestesiol* 2018;84:157–8.
9 Ballard C, Jones E, Gauge N, *et al*. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. *PLoS One* 2012;7:e37410.
10 Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly - what are the differences? *Minerva Anestesiol* 2011;77:742–9.
11 Glumac S, Kardum G, Sodic L, *et al*. Effects of dexamethasone on early cognitive decline after cardiac surgery: a randomised controlled trial. *Eur J Anaesthesiol* 2017;34:776–84.
12 Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth* 2009;103 Suppl 1:i41–6.
13 Wu CL, Hsu W, Richman JM, *et al*. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. *Reg Anesth Pain Med* 2004;29:257–68.
14 Deiner S, Luo X, Silverstein JH, *et al*. Can intraoperative processed EEG predict postoperative cognitive dysfunction in the elderly? *Clin Ther* 2015;37:2700–5.
15 Steinmetz J, Funder KS, Dahl BT, *et al*. Depth of anaesthesia and post-operative cognitive dysfunction. *Acta Anaesthesiol Scand* 2010;54:162–8.
16 Langer T, Santini A, Zadek F, *et al*. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. *J Clin Anesth* 2019;52:111–8.
17 Forsberg A, Cervenka S, Jonsson Fagerlund M, *et al*. The immune response of the human brain to abdominal surgery. *Ann Neurol* 2017;81:572–82.
18 Terrando N, Eriksson LI, Ryu JK, Kyu Ryu J, *et al*. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011;70:986–95.
19 Sauër A-M, Kalkman C, van Dijk D. Postoperative cognitive decline. *J Anesth* 2009;23:256–9.
20 Steinmetz J, Christensen KB, Lund T, *et al*. Long-Term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009;110:548–55.
21 Creswell JW. Controversies in mixed methods research. The SAGE Handbook of qualitative research 2011;4:269–84.
22 Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. *Köln Z Soziol* 2017;69:107–31.
23 Silbert B, Evered L, Scott DA, *et al*. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology* 2015;122:1224–34.
24 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
25 Nilsson U, Dahlberg K, Jaensson M. The Swedish web version of the quality of recovery scale adapted for use in a mobile APP: prospective psychometric evaluation study. *JMIR Mhealth Uhealth* 2017;5:(e188).
26 Lundeberg T, Lund I, Dahlin L, *et al*. Reliability and responsiveness of three different pain assessments. *J Rehabil Med* 2001;33:279–83.
27 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
28 Moffatt S, White M, Mackintosh J, *et al*. Using quantitative and qualitative data in health services research - what happens when mixed method findings conflict? [ISRCTN61522618]. *BMC Health Serv Res* 2006;6:28.
29 Krenk L, Kehlet H, Bæk Hansen T, *et al*. Cognitive dysfunction after fast-track hip and knee replacement. *Anesthesia & Analgesia* 2014;118:1034–40.
30 Association WM. World Medical association Declaration of Helsinki. ethical principles for medical research involving human subjects. *Bull World Health Organ* 2001;79.
31 Barron JP. The uniform requirements for manuscripts submitted to biomedical journals recommended by the International Committee of medical Journal editors. *Chest* 2006;129:1098–9.

BMJ Open

Understanding neurocognitive recovery in older adults after total hip arthroplasty: neurocognitive assessment, blood biomarkers, and patient experiences - a mixed methods study.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-093872.R1
Article Type:	Original research
Date Submitted by the Author:	18-Dec-2024
Complete List of Authors:	Amirpour, Anahita; Karolinska Institutet, Neurobiology, Care Sciences and Society Bergman, Lina; Karolinska Institute, Neurobiology, care sciences, society Markovic, Gabriela; Karolinska Institutet, Department of Clinical Sciences; Danderyd University Hospital, Department of Rehabilitation Medicine Liander, Karin; Karolinska Universitetsjukhuset i Huddinge, Perioperative Medicine Intensive care Nilsson, Ulrica; Karolinska Institutet, Neurobiology, Care Sciences and Society Eckerblad, Jeanette; Karolinska Institute, Neurobiology, Care sciences, society
Primary Subject Heading:	Geriatric medicine
Secondary Subject Heading:	Anaesthesia, Rehabilitation medicine, Surgery
Keywords:	NEUROLOGY, ORTHOPAEDIC & TRAUMA SURGERY, Old age psychiatry < PSYCHIATRY

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Understanding neurocognitive recovery in older adults after total hip arthroplasty: neurocognitive assessment, blood biomarkers, and patient experiences - a mixed methods study.

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Acknowledgments: We thank Jennifer Kanon, Professor Lars. I Eriksson, Professor Lars Rasmussen, Professor Olav Rooijackers, Dr. Harald Brismar and all health care professionals at the hospital for their assistance. Extra thanks to the patients who participated in our study.

Abstract:

Objective: Delayed neurocognitive recovery, previously known as postoperative cognitive dysfunction, is a common complication affecting older adults after surgery. This study aims to address the knowledge gap in postoperative neurocognitive recovery by exploring the relationship between subjective experiences, performance-based measurements, and blood biomarkers.

Design: Mixed methods study with a convergent parallell (QUAL+quan) design.

Setting and Participants: The study report results from 40 older adult patients (52.5% women; mean age 73, SD=6.7), scheduled for total hip arthroplasty at a hospital in Sweden.

Outcome measures: Neurocognitive performance was assessed using a standardized test battery, neuroinflammation through blood biomarker analysis, and postoperative neurocognitive recovery via semi-structured interviews and the Swedish Quality of Recovery questionnaire.

Results: Five patients were classified as having delayed neurocognitive recovery based on performance tests. Qualitative data revealed that most patients reported cognitive symptoms, mainly, particularly related to executive functions and fatigue. Psychological factors, including a sense of agency and low mood significantly influenced cognitive recovery and daily functioning. Elevated inflammatory blood biomarkers were not detected pre- or postoperatively in patients with delayed neurocognitive recovery. The global postoperative recovery score was 40.9, indicating a low quality of recovery.

Conclusion: Many patients reported subjective cognitive decline that was not corroborated by delayed neurocognitive recovery in the performance-based tests. Psychological factors were influential for neurocognitive recovery and should be routinely assessed. Future research should incorporate longitudinal follow-ups with performance-based measurements, fatigue assessment, evaluations of instrumental activities of daily living, and subjective reporting, supported by a multidisciplinary team approach.

Clinical Trial Registration: NCT05361460

Keywords: arthroplasty, replacement, hip, neurocognitive disorders, neuropsychological tests, postoperative cognitive complications

Article summary

Strengths and limitations of this study

- To our knowledge, this is the first mixed methods study exploring performance-based measurements and subjective reports of postoperative neurocognitive recovery after orthopedic surgery.

- We assessed neurocognitive performance with a test battery, explored postoperative neurocognitive recovery through semi-structured interviews and measured the potential neuroinflammatory response with blood biomarkers.
- Results from 40 patients at a university hospital in Sweden are presented, a sample that may not be generalizable to other contexts.

Competing interests: None.

Ethical approval: We obtained ethical permit (2019-02968) from the Swedish Ethical Review Authority on 2019-06-19. The study followed the Declaration of Helsinki.

Informed consent: All participants received oral and written information about the study, and written consent was obtained from all participants.

Funding statement: This work was supported by The Research school in Health science, Karolinska Institutet grant number [2020-02641]; and Strategic Research Area Health Care Science, Karolinska Institutet grant number [2-1742/2021].

1. Introduction

Delayed neurocognitive recovery (dNCR), formerly known as postoperative cognitive dysfunction (POCD) [1] commonly affects older adults within a month post-surgery [2 3] Neuroinflammation and oxidative stress has been demonstrated to be part of the mechanism of dNCR [4 5], and proinflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha enter the brain via normal or disrupted blood-brain-barrier [6]. Yet, at present there are no specific inflammatory biomarkers clinically validated for predicting or diagnosing dNCR [5]. Moreover, fluctuations in tryptophan plasma levels have been suggested as a potential cause of postoperative fatigue, affecting serotonin 5-HT production and contributing to postoperative fatigue through 5-HT-synthesis resulting from changes in plasma amino acid levels [7].

The recovery process from surgery is a multifaceted construct influenced by physical, psychological, and social factors [8]. Patients may regain their preoperative state or surpass it, reaching a high level of well-being and recovering lost functions[8 9]. While perioperative research has emphasized overall recovery, the understanding of neurocognitive recovery in particular—what it entails, how it is experienced, and its implications—remains ambiguous.

Delayed neurocognitive recovery manifests with cognitive decline in memory, attention, processing speed, and executive functions [1], and is linked to heightened disability risk [10]. Traditionally, dNCR was assessed only through neurocognitive tests [11] but the updated nomenclature includes subjective cognitive decline (SCD) and daily function changes in the diagnosis [1]. SCD, reported even without cognitive impairment, indicates elevated future cognitive impairment and dementia risk [12]. However, perioperative research has primarily focused on quantitative measures of dNCR in the past decades, resulting in subjective reports being overlooked.

Therefore, this mixed methods study aims to fill the current knowledge gap in postoperative neurocognitive recovery by integrating quantitative and qualitative data. By exploring performance-based measurements (neurocognitive test battery), blood samples (biomarkers) and how subjective reports on neurocognitive recovery (semi-structured interviews and a patient-reported outcome) are experienced. We hypothesized that patients showing decline in performance-based tests would have differing experiences in the interviews, and vice versa.

2. Methods

Study design and setting

This mixed-methods study, had a parallell convergent (QUAL+quan) design [13 14], and was conducted at a university hospital in Stockholm, Sweden. The mixed methods design was qualitatively dominant, and we integrated both qualitative and quantitative approaches [15] with the intention to provide an in-depth understanding of early postoperative neurocognitive recovery, following the Diagnostic and Statistical Manual of Mental disorders fifth edition (DSM-5) criteria for mild/major neurocognitive disorders [16] . We collected and analyzed the quantitative and qualitative data separately, subsequently merged to identify any convergences, divergences, or relationships between the two.

We obtained ethical permit (2019-02968) from the Swedish Ethical Review Authority on 2019-06-19, registered the study at ClinicalTrials.gov (NCT05361460), and published the study protocol [17]. We recruited patients at the scheduled clinical preoperative visit, provided study information, and obtained written informed consent from all patients, following the Declaration of Helsinki [18].

Study population

Between October 2019 and November 2021, we included 46 patients aged ≥60 years through convenience sampling. There were 6 dropouts (Figure 1). Recruitment was extended by 18 months due to the COVID-19 outbreak. All potential eligible study participants were preliminary screened and approached by the fourth author. The patients were scheduled for total hip arthroplasty and all patients underwent both the quantitative and qualitative data collection. Exclusion criteria were: Mini Mental State Examination (MMSE)[19] ≤22, nervous system disease, dependence on antidepressant or tranquilizer, alcohol or drug misuse, hearing or visual impairment, surgery in the previous 6 months, and lack of fluency in Swedish.

Outcome measures

We obtained demographic and perioperative data from patient records, including comorbidities, age, sex, MMSE score, pain intensity with numeric rating scale (NRS), education level, cohabitant status, American Society of Anesthesiologists classification (ASA-classification), anesthetic technique and duration, and duration of the surgery.

Neurocognitive assessment

We measured neurocognitive performance with the International study of postoperative cognitive dysfunction (ISPOCD) test battery [20], administered by the fourth author, who was trained in neurocognitive testing. The battery includes four neurocognitive tests [20]:

1. **Visual Verbal Learning Test (VVLT)** measuring verbal episodic memory, based on Rey's auditive recall of words, includes 15 words in 3 trials. A higher total word count indicates better scores.
2. **Concept Shifting Test (CST)**, measuring visual mental flexibility, based on the Trail Making Test includes 16 circles in 3 trials. Less time and fewer errors indicate better scores.
3. **Letter-Digit Coding Test (LDC)**, measuring executive attention, working memory and speed, based on the Symbol Digits Substitution Test during 60 seconds. High scores indicate better performance.
4. **Stroop Colour-Word Test (SCW)**, measuring executive selective attention, includes 40 words in 3 trials. Less time and fewer errors indicate better scoring.

Patient reported outcome measurement

We assessed postoperative quality of recovery with the 24-item Swedish quality of recovery questionnaire (SwQoR-24). Each item measures various symptoms or discomfort related to surgery and anesthesia such as pain, nausea, anxiety, sleep difficulties, fatigue. The patient rates these items on an 11-item scale, ranging from 0 (indicating none of the time) to 10 (indicating all the time). The range is from 0, indicating excellent quality of postoperative recovery, to 240, indicating poor quality of postoperative recovery. The patient is considered to have a good postoperative recovery if they have a global score less than 21 on postoperative day 14. The SwQoR-24 has been validated in a Swedish setting with postoperative patients [21 22].

Blood-borne biomarkers

We measured inflammatory biomarkers Granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon gamma (IFN-ɣ), interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-6 (IL-6), (IL-8), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α), and the non-inflammatory biomarker Tryptophan at the preoperative visit, postoperative day 1 and on day 13-16 to assess its association with neurocognitive recovery. We took peripheral blood (11 mL

whole blood) from the patient, centrifuged it, and plasma was stored at -80 degrees Celsius until analysis. Tryptophan was measured using the standardized technique High Performance Liquid Chromatography (HPLC). We analyzed all blood samples in August 2023, with the BIO-RAD Bio-Plex Pro Human Cytokine 8-plex Assay #M50000007A.

Procedure

The preoperative assessment at the orthopedic clinic included a performance-based measurement using a standardized test battery (ISPOCD), blood sampling, and SwQoR-24.The postoperative assessment on days 1 to 3 included blood sampling and SwQoR-24. On day 13 to 16, the postoperative assessment at the orthopedic clinic included the test battery, blood sampling, SwQoR-24, and semi-structured qualitative interviews. This timeline was selected to capture delayed neurocognitive recovery, which is manifested within 30 days after surgery [23].

Surgery and anesthesia

The total hip arthroplasty surgery was carried out in accordance with normal clinical practice. Patients received spinal anesthesia, either with 0.25 ml morphine (0.4 mg ml) and 2.8 ml bupivacaine (5 mg ml) at level L3–L4 or L2-L3, or with 3.5 ml bupivacaine (5 mg ml) only. Four patients underwent general anesthesia with tracheal intubation, using a combination of induction drugs such as Alfentanil, Propofol, Fentanyl and a variation of neuromuscular blocking drugs, and maintenance anesthesia with Sevoflurane.

Qualitative data

Semi-structured, face-to-face interviews were conducted two weeks after surgery. The interview questions covered cognitive functions, daily activities, and overall mood, following an interview guide (Supplementary Material 2). Each interview was audio-recorded and transcribed verbatim.

Data analysis

Statistical analysis

Descriptive statistics are presented as means, standard deviations, median score, and completion times for the neurocognitive test battery. Wilcoxon signed rank test was applied to assess changes in raw scores and completions times for the neurocognitive test battery. Normality of the data was assessed with Q-Q plots, histograms and Shapiro Wilk Test. A two-sided p-value of <0.05 was considered statistically significant. Cognitive performance

changes were adjusted for practice effects and variability using age-matched nonsurgical controls, the z-scores were calculated to assess changes from preoperative to postoperative tests with dNCR defined as a z-score of ≥1.0 on day 13-16 after surgery, z-score of <1.0 on day 13-16 indicated no decline according to the ISPOCD method [20] We followed the diagnostic rule for delayed neurocognitive recovery, meaning decline in at least two sub-tests [11]. We used IBM SPSS version 28 (IBM Corp., Armonk NY) for statistical analysis.

Qualitative analysis

Four authors (AA, GM, JE, LB) analyzed the qualitative data. We applied Elo & Kyngäs [24] description of content analysis to the data, with a deductive and inductive approach. We initially chose a set of categories i.e., cognitive domains; attention and memory and, executive functions based on theoretical framework [25], and our research objectives. These categories served as a structured matrix to code the data. As our analysis advanced, we recognized a recurring affective theme in the interviews. We openly coded these meaning units and categorized them as psychological factors, aligning with our research questions and acknowledging their influence on neurocognitive recovery. The analysis process involved several iterative steps. First, we read the verbatim transcribed interviews thoroughly. Then, we developed a structured categorization matrix (Supplementary Material 1), and reviewed and coded the data according to the categories and subcategories, and only extracted data that fit the final matrix [24]. Lastly, we held meetings regularly within our research group to achieve an agreement on data analysis.

Mixed methods analysis

First, we analyzed the qualitative and quantitative datasets separately. Then, we merged the results from the datasets by conducting a thorough side-by-side comparison, which is visualized in the joint display (Table 3) [26]. The joint display comparison enabled us to assess for confirmation, discordance, and expansion of the datasets, and draw meta-inferences [26]. All findings were discussed within the research group. The initial proposed display was created by AA through an iterative process, with patterns, revisions and reviews conducted by LB and GM.

Patient and public involvement

Patients and public were not involved in the design, conduct, reporting or dissemination of this research.

3. Results

This section starts with patient characteristics based on assessment data including biomarkers, followed by domain-level findings on executive functions, attention and memory, and psychological factors. In the Discussion section, the integrated results are further expanded through a joint display (Table 3).

Patient characteristics and perioperative data

Six patients were excluded from the analyses because of withdrawn participation, postoperative complications, surgery elsewhere and the research team not being available, thus leaving 40 patients (Figure 1). Patient characteristics and test results on a group level are presented in Table 1 and 2.

Neurocognitive assessment

Among the 40 patients, five were classified as dNCR (z-score >1.0 in at least two sub-tests), with no statistical differences in anesthetic factors or characteristics between those with/without dNCR. The mean scores and relevant completion times for each sub-test are presented in Table 2.

Patient reported quality of recovery

On postoperative day 14, the patients' postoperative recovery global score was mean 40.9 (Table 1) indicating low quality of recovery. There were no differences in SwQoR-24 scores between those with/without dNCR.

Blood borne biomarkers

One patient did not have a preoperative inflammatory biomarker result, and three patients had missing results on the first postoperative day. The cytokines GM-CSF, IFN-γ, IL-10, IL-2, and IL-4 were undetectable in all patients, while IL-6, IL-8, TNF-α were detectable but below 0 pg/mL. Tryptophan levels (Table 1) were low both preoperatively and postoperatively in the total sample.

Executive Functions

Among the participants, n=12/40 declined on the Stroop Color Word test, n=10/40 on the Concept Shifting Task test, and n=8/40 on the Letter Digit Coding test (Table 3). Moreover,

in the interviews (Supplementary material 1), the most significant and frequent problems the patients described was related to their executive functions. The main qualitative findings were associated to *Problem-solving, Emotional regulation, Energization and Fatigue.*

These challenges manifested considerably when patients tried to resume their everyday activities at home or work, including meal preparation and initiating social contacts. While some patients dedicated effort to their physical rehabilitation, others refrained due to energy constraints, recounting days spent entirely in bed.

The patients described developing new strategies and skills to deal with the current changed form, where some patients learned to carry the mug in another way, using a basket to carry the plate with food to the bed to eat, using a ladder with help from spouse or if the patient was living alone, this also affected their strategy, doing the task independently:

> *And I have learned to walk, so that it works. But it was an effort I didn't think I would have to make. But it was the first time in these 50 years that I feel strained* (P01).

The effort to sustain energy to certain activities became particularly apparent in patients living with spouses or children, as these family members assumed every task, from dressing to household chores. Patients struggling with these limitations often experienced emotional turmoil, expressing anger, impatience, and frustration upon realizing their changed capacity for simple everyday tasks:

> *I've been a bit grumpy, I guess. I don't need to hide that. But no one has taken offense. I've tried to be kind and nice, but sometimes you just snap a bit* (P10).

These issues with regulating emotions were previously unfamiliar to the patients and sometimes led to strained relationships, as some patients vented their emotions on their spouses.

The patients' coping mechanisms varied, with some patients testing how far they could go in attempting pre-surgery activities such as leaving the house and go on a walk. Conversely, others embraced their current limitations, recognizing the futility of certain tasks during this phase of recovery. The patients conveyed a profound sense of fatigue or lethargy, irrespective of what they did or following specific activities. This fatigue was articulated on either cognitive and motoric domain, or both:

> *The only thing I've managed is to go to the bathroom and take care of my needs and... yes, brush my teeth and things like that. […] I can handle such tasks, but nothing else. I don't have the energy for it, I'm too tired. […] I couldn't even dress myself at first. My husband had to help me get dressed, you know* (P06).

In response to this fatigue, patients adopted alternative coping mechanisms. Some patients resorted to daytime sleeping while others avoided activities. This avoidance, distinct from their pre-surgical behaviour, was characterized by patients refraining from planned activities. For instance, they reported a shift from an intention to tidy up the house to do nothing at all. Similarly, they described avoiding interactions with friends or family members due to a lack of energy to engage in conversations.

Attention and Memory

In the Visual Verbal Learning test, n=4/40 patients declined. The main qualitative findings were related to *Subjective or Family concerns of Memory decline, Sustained attention, and Mind wandering.*

Patients frequently described instances of forgetfulness, such as entering the kitchen or bathroom and subsequently forgetting their intended tasks. Some explicitly acknowledged memory decline, recognizing pre-existing issues even before surgery. Patients who experienced forgetfulness occasionally questioned themselves, speculating whether such lapses existed before surgery.

> *Yes, I feel like I've had a really poor memory for a long time now. Because I've been anxious about the surgery, and that affects concentration a bit. And I haven't been feeling very well before either (P07).*

Others recognized their memory decline to aging. For example, one patient expressed family concern, revealing that a family member had commented on his memory loss recently. As a result, the family member had taken over tasks the patient once handled independently. Consequently, the patient articulated he perceived a memory loss.

Some patients described how their minds wandered, especially during activities like reading, or showering leading to difficulties in sustaining their attention. As a result, they often abandoned the task. In contrast, others created adaptive strategies to manage their focus and

memory, such as pre-planning their medication routine and organizing pills in specific containers.

Psychological factors

The main qualitative findings were related to *Sense of agency, powerlessness, physical limitations, and future perspectives.*

In the interviews, some patients expressed a sense of relief and improved well-being post-surgery, assigning it to the resolution of long-term pain that had accompanied every movement before surgery. This positive change had a notable impact on their mood, as they reflected on their pre-surgery state characterized by persistent pain.

> *I feel much more positive now than right after the surgery, as I sense that the pain is heading in the right direction, and the mobility in the operated leg also feels much better, in that way. So, I feel that I am regaining a bit more zest for life compared to before the surgery* (P03).

On the contrary, other patients conveyed feelings of powerlessness and dependence on family members post-surgery, particularly in managing daily activities. Despite their family members' well-intentioned efforts to protect them, this gave rise to annoyance. The patients had a desire to maintain a sense of agency even though their abilities had changed post-surgery. This transition from independent functioning to reliance on others resulted in feelings of despair or a bad mood:

> *…To 110%. I don't want to be dependent…Yes, I become disheartened and a little angry, and... What should I say?... Just this being dependent, it's... Yes, I want to do everything myself if I may say so. Control my day, or control and manage and so on* (P08)

Expectations for the future and the ability to function independently raised concerns, especially regarding the possibility of driving a car again. These worries about the future, coupled with doubts about improvement, led to mood disturbances such as irritability and feeling low.

> *I have a different way, a different temperament. I don't recognize myself. I am sometimes sad, and that's not something I used to be* (P46).

Several patients spoke about the significant shift from being in control pre-surgery to a postoperative state where they felt a loss of control over their bodies, their capabilities, and a sense of being different. This perceived loss of control within the healthcare system left patients feeling exposed.

4. Discussion

We explored how 40 older adult patients experienced neurocognitive recovery after total hip arthroplasty and how this experience aligned or differed with neurocognitive assessment and biomarker results. Interestingly, no apparent differences were observed between those with detected dNCR and those without, whether in qualitative or quantitative data collection. Consequently, the data was presented at the group level.

In the neurocognitive tests, only five patients were classified as dNCR. However, more patients showed impairments in individual cognitive domains. This indicates that, although they did not meet the criteria for dNCR, they still experienced some degree of cognitive impact. Among patients classified as having dNCR, no specific subjective complaints or expressions of worry were reported during the interviews. Moreover, subjective cognitive decline was widely expressed by many patients in the interviews. The incongruence between the objective test results and subjective cognitive decline is anticipated [27], as the controlled neurocognitive test environment lacks external distractions compared to home or the workplace. Patients may demonstrate normal cognitive performance briefly during the test, but their day-to-day functioning could be compromised, leading to subjective cognitive decline [28] which became noticeable in the qualitative data. Furthermore, our findings align with previous research that discovered no correlation between cognitive performance and self-reported cognitive complaints [2 28-30]. Nonetheless, subjectively reported data in perioperative research is often obtained with a variability of methods, such as questionnaires [30], phone interviews post-surgery [29 31], or a single-item binary question [2]. The variability in data gathering poses a substantial challenge in consolidating findings and identifying comprehensive patterns. The diverse definitions and measurement approaches for SCD further complicate this task. In contrast, aging research on SCD has primarily focused on symptom type and intensity, with a higher symptom burden increasing the risk of clinical progression [32].

We found no association between inflammatory biomarkers and dNCR, consistent with other studies [33-35]. As the inflammatory biomarkers were either undetectable or below 0 pg/L, they were excluded from data integration. Previous studies vary in their results when using inflammatory biomarkers to detect dNCR, these variations may be due to different types of surgery and different methods of analysing inflammatory markers. For example, a meta-analysis [33] revealed an association between elevated C-reactive protein levels in both

postoperative delirium and cognitive decline. However, insufficient evidence was available to draw conclusions regarding IL-6, while IL-8, IL-10, and TNF-α showed no significant association with cognitive decline. Similarly, a recent systematic review [36] noted elevated IL-6 levels within <12 hours postoperatively in older adults but found no such association for TNF-α. Another study focusing on older adults after hip fracture surgery, indicated that glucocorticoid administration reduced levels of IL-6 and TNF-α. [37]. Perioperative administration of glucocorticoids, commonly used in orthopedic surgery, and non-steroidal anti-inflammatory drugs (NSAID), frequently prescribed for osteoarthritis [38], have been found to suppress cytokines including IL-6 and TNF-α [39]. Aligning with these findings, updated European guidelines on postoperative delirium advise against the use of biomarkers for prediction or prevention of delirium in patients at-risk [30]. Nevertheless, it remains uncertain whether this recommendation extends to delayed neurocognitive recovery, posing implications of the design of future trials.

Tryptophan levels were consistently low in our patients, similar to findings in a study of patients with cancer-related fatigue [40]. Interestingly, mean tryptophan levels in other studies were higher: 74.4 µM in patients with cancer-related fatigue [41] and 65 µmol/L in bariatric surgery patients [42]. Besides the serotonin pathway, tryptophan is catabolized in the kynurenine pathway and plays a role in energy homeostasis. Changes in this pathway can be associated with low grade inflammation [41] which is relevant to our patient group with osteoarthritis, a chronic inflammatory condition. Postoperative fatigue, characterized by persistent weakness or tiredness is frequently overlooked, and significantly impacts cognitive, behavioral and physical functions, often delaying the resumptions of daily activities after surgery [43]. We found that two of the most frequently described symptoms in the qualitative data was lack of energy and lethargy impacting the patient's daily functioning after surgery, aligning with previous research [44]. However, we did not ask how their energy levels were before the surgery. Lethargy and lack of energy may be interpreted as fatigue which is not traditionally a component in neurocognitive tests even though it impacts cognitive functioning. Assessment of postoperative fatigue can be a helpful element, in addition to neurocognitive assessments to predict postoperative recovery. Furthermore, each meaning unit from the qualitative data may not exclusively correspond to a singular cognitive domain but can in fact match to more than one, such as subjective complaints about attention could match with memory. Previous literature indicate attention, working memory, and executive control share substantial similarities in their functional and structural neural correlates [45].

Postoperative pain was well-controlled, as evidenced by the low pain scores. While some patients described an improved sense of well-being after experiencing pain relief following surgery, others expressed concerns about the future and the ability to function independently. The different coping strategies which the patient employed to resume daily activities aligns with earlier studies [44 46 47]. In our study, patients described low mood, dependency on others and perceived loss of agency which impacted their daily functioning due to the surgery. Earlier studies [44 47-49] have found that psychological factors, specifically vulnerability factors like depressive and anxiety symptoms affect postoperative recovery. These factors not only manifest behaviourally through avoidance behaviours but also have cognitive implications [50]. Patients described how social support facilitated a smoother postoperative recovery process. Social support is related to improved global cognitive function, executive functions and memory [51]. In our study, most patients resided with a spouse and received support in their daily activities e.g., help with dressing, and cleaning. On the other hand, some patients expressed a sense of powerlessness due to their reliance on others. For them, depending on external support symbolized discomfort in seeking help. Therefore, clinical implications should include assessing surgical patients for emotional stress, such as depression and anxiety, as these factors are important predictors of postoperative recovery. Behavioural therapeutic interventions can be effective in addressing these concerns [52].

The mean postoperative recovery score (SwQoR-24) was 40.9 on a group level, meaning they had a higher postoperative symptom burden and low quality of recovery, whereas a score <21 on postoperative 14 , would indicate they had a good postoperative recovery [22]. However, the quality of recovery score in the referenced study pertains to a day surgery unit with a mix of young and older patients, which may not be directly applicable to our group consisting of older adults with comorbidities.

To our knowledge, this is the first mixed-methods study exploring delayed neurocognitive recovery together with psychological factors after total hip arthroplasty. All participants underwent qualitative interviews, blood tests, and neurocognitive tests, and our results present detailed descriptions of postoperative neurocognitive and emotional recovery. We acknowledge the limitations of this study. This include strict eligibility criteria which led to the exclusion of many patients, and may have excluded frailer individuals, e.g., those with nervous system diseases. Generalizability of our results is limited due to a small number of participants, and the convenience sampling is also a limitation. Further, this study lacked a

standardized delirium assessment while patients were at the hospital and a preoperative depression screening. However, the SwQoR-24 does include items assessing anxiety and depressive symptoms. While we acknowledge the potential for bias with the same person conducting both tests and interviews, efforts were made to minimize bias by standardizing the test procedure and instructions provided to all participants.

Future direction should involve multidisciplinary teams that bridge specialty, primary, and social care services. Long-term follow-ups should include objective neurocognitive assessments, evaluations of fatigue, and measurements of instrumental daily activities. Additionally, patients' subjective reports must be gathered in accordance with recommended terminology [1].

Conclusion

We found a disparity between subjective reports of neurocognitive recovery and performance-based measurements. Only five patients were classified as having delayed neurocognitive recovery, however many patients described changes in their daily functioning due to cognitive and psychological symptoms. Our study highlights the complexity and breadth of postoperative neurocognitive recovery which extends beyond psychometric testing and blood samples.

Authors contribution

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Figure 1: Flow chart of participants

Table 1. Patient characteristics.

	Total sample (n=40)
Sex	
Men, n (%)	19 (47.5)
Women, n (%)	21 (52.5)
Age, years	
Mean (SD)	73 (6.7)
Min-max	60-87
Level of education	
Elementary school, n (%)	11 (27.5)
Upper secondary school, n (%)	13 (32.5)
Tertiary education, n (%)	16 (40)
Living situation	
Lives with spouse or adult children, n (%)	29 (72.5)
Lives with spouse and has home care, n (%)	1 (2.5)
Lives alone, n (%)	9 (22.5)
Lives alone and has home care, n (%)	1 (2.5)
MMSE	
Mean (SD)	28 (1.4)
ASA	
I, n (%)	5 (13)
II, n (%)	18 (45)
III, n (%)	17 (42)
Comorbidities	
Heart disease (e.g., hypertension) n (%)	24 (57)
Vascular disease, n (%)	9 (21)
Lung disease, n (%)	6 (14)
Kidney disease, n (%)	1 (2)
Diabetes, n (%)	5 (12)
History of cancer, n (%)	8 (19)
Autoimmune disease, n (%)	6 (14)
Type of anesthesia	
Spinal, n (%)	36 (90)
General, n (%)	4 (10)
Duration of surgery, minutes (SD)	114.5 (32.4)
Duration of anesthesia, minutes (SD)	188.5 (36.5)
Intraoperative bleeding, ml (SD)	348 (148.9)
Postoperative days at the hospital, mean (SD)	1.5 (0.6)
Preoperative pain, NRS, mean (SD)	5.4 (3.2)
Postoperative pain day 14, NRS mean (SD)	2.1 (2.1)
Preoperative tryptophan µmol/l mean (SD)	43.8 (9.5)
Postoperative tryptophan µmol/l day 13-16 mean (SD)	41.9 (10).
QoR global score, day 13-16 mean (SD)	40.9 (28.4)
Postoperative opioid treatment, day 14	
Yes, n (%)	17 (43)
No, n (%)	23 (57)

Abbreviations: MMSE= Mini Mental State Examination; ASA= American Association of anesthesiologists' physical status classification system, NRS=Numeric rating scale, QoR=quality of recovery

Table 2. Summary of the patients' raw scores and completion times on the neurocognitive tests

	Preoperative measurement **Mean (SD)** **Median**	**Postoperative measurement** **Mean (SD)** **Median**	*p-value**
VVLT total word count	22.3 (5.0) Med: 22.0	25.3 (5.9) Med: 25.5	<0.05
VVLT delayed recall, total word count	8.1 (2.6) Med: 8.0	9.1 (3.2) Med: 9.5	<0.05
CST, time (s), part C	38.8 (14.8) Med: 33.1	36.9 (13.5) Med: 35.4	0.49
CST, number of errors, part C	1.4 (2.7) Med: 0	1.1 (2.2) Med: 0	0.42
LDC, score	27.4 (5.9) Med: 28	27.9 (7) Med: 30	0.39
SCW, time (s), part 3	51.4 (19.2) Med: 47.5	50.3 (22.1) Med: 43,8	0.15
SCW, number of errors	0.6 (1) Med: 0	0.9 (1,9) Med: 0	0.22

Abbreviations: VVLT=Visual Verbal Learning Test; CST=Concept Shifting Task; LDC=Letter Digit Coding Test; SCW=Stroop Color Word Test
*Wilcoxon signed rank test.

Table 3. Joint display presenting quantitative, qualitative and mixed-methods meta-inferences of domains.

MM domains	**Quantitative findings** **Number of patients with** z-score ≥1.0 i.e., delayed neurocognitive recovery on neurocognitive tests.	**Qualitative findings** **Codes and quotes**	**Meta-inferences**
Executive functions	Stroop Color Word Test (SCW), n=12/40 Concept Shifting Task (CST), n=10/40 Letter Digit Coding Test (LDC), n=8/40	*Performance awareness* So, you learn a lot of tricks, you stand in a corner, brace yourself against your back and stand on the leg you can put weight on. Yeah, then you can play around with the coffee maker (P43). *Having a short fuse* So, I have a pretty short fuse, and I lose patience when things don't go smoothly... like when I can't put on my pants and stuff, so then I get angry. And then it might happen that a crutch ends up in the wall or something (P31) *Not thorough as before and delaying action* I notice that's not like me. I am very thorough about everything. But now, there are things everywhere, and, by the way, it's hard to pick up. But I think, well, I'll do that later. But I haven't done it yet (P08). *Motoric fatigue* I am tired, physically ... if I go out and walk, as I have tried to do for the last three days…then I am quite tired afterwards…Yes, it's time to lie down. And then I'm not really fit for fight ... I don't have much energy for the rest of the day (P31)	In the performance-based tests, only a small number of patients declined on the tests. Fatigue was not addressed in the neurocognitive tests. However tryptophan levels were overall low in the total sample. Moreover, the qualitative data brought to light significant changes in patients' daily functioning, including changes in their performance at home or at work. Patients described new challenges in emotional regulation, where they would become frustrated or have angry outbursts on their family members. Some patients described a fatigue-like state, leading them to spend entire days in bed.

Attention **Memory**	Visual Verbal learning test (VVLT), n=4/40	*Doubting memory function* But, you know, it's just that you start to think that you're not sure when you yourself stop noticing that you forget things (P05). *Family member pointing out memory decline* If I have experienced some memory loss, it's possible, it's possible. Because our children said, 'Dad, you won't remember this. It was like this' (P01). *Feeling absent-minded* So right now, I can read and read and read, and still, I find myself stuck on the same sentence, and then and then it's just as good to leave it […] Uhm, concentration, I can't concentrate properly (P10).	The test evaluated episodic memory at a specific point in time and demonstrated the lowest number of patients declining. The qualitative data showed that patients described attentional changes over time, with only a few acknowledging subjective memory decline or expressing family concerns about memory decline. Feelings of absent-mindedness and a lack of focus were identified as factors influencing both their memory and decision-making regarding the activities they chose to engage in or avoid.
Psychologica **l factors**		*Wanting to manage things independently* Sometimes it's my dear wife... I become more easily irritated, perhaps. It has to do with her trying to be overly protective and fetch everything for me, and I think to myself, "I can handle this on my own," and then I get slightly annoyed at trivial things that are not relevant (P03) *Being in a bad mood and dependant on others* And the thing about being dependent on other people and... you don't want to bother people, even if they're your own sons, it feels like 'God, how annoying I am.' And then I get in a bad mood (P19). *Feeling low* I feel a bit depressed because I can't do anything, and not fix anything, not fetch anything, not pick up anything (P08) *Brighter outlook* I think maybe I was grumpier before the surgery than after, because now it's done. And now, well, theoretically at least, it can't get worse. Now it's just going to get better (P12)	While performance-based measures focus solely on level of cognitive functions, they fall short in capturing the affective components. In the qualitative data psychological factors was expanded upon, with patients articulating the impact of factors such as the sense of agency, feelings of powerlessness stemming from dependence on others, and adjustments to new physical limitations. These factors not only shaped their overall well-being but also significantly influenced their relationships and daily functioning. Conversely, a few patients shared a more optimistic perspective on life, attributing it mainly to the relief from previous pain.

References

1. Evered L, Silbert B, Knopman DS, et al. Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery-2018. *Anesthesiology* 2018;129(5):872-79. doi: 10.1097/aln.0000000000002334
2. Deiner S, Liu X, Lin HM, et al. Subjective cognitive complaints in patients undergoing major non-cardiac surgery: a prospective single centre cohort trial. *Br J Anaesth* 2019;122(6):742-50. doi: 10.1016/j.bja.2019.02.027 [published Online First: 2019/04/21]
3. Evered L, Atkins K, Silbert B, et al. Acute peri-operative neurocognitive disorders: a narrative review. *Anaesthesia* 2022;77 Suppl 1:34-42. doi: 10.1111/anae.15613 [published Online First: 2022/01/11]
4. Safavynia SA, Goldstein PA. The Role of Neuroinflammation in Postoperative Cognitive Dysfunction: Moving From Hypothesis to Treatment. *Front Psychiatry* 2018;9:752. doi: 10.3389/fpsyt.2018.00752 [published Online First: 2019/02/02]
5. Evered LA, Silbert BS. Postoperative Cognitive Dysfunction and Noncardiac Surgery. *Anesthesia & Analgesia* 2018;127(2):496-505. doi: https://dx.doi.org/10.1213/ANE.0000000000003514
6. Li Z, Zhu Y, Kang Y, et al. Neuroinflammation as the Underlying Mechanism of Postoperative Cognitive Dysfunction and Therapeutic Strategies. *Front Cell Neurosci* 2022;16:843069. doi: 10.3389/fncel.2022.843069 [published Online First: 2022/04/15]
7. McGuire J, Ross GL, Price H, et al. Biochemical markers for post-operative fatigue after major surgery. *Brain Res Bull* 2003;60(1-2):125-30. doi: 10.1016/s0361-9230(03)00021-2
8. Nilsson U, Jaensson M, Hugelius K, et al. A journey to a new stable state-further development of the postoperative recovery concept from day surgical perspective: a qualitative study. *BMJ Open* 2020;10(9):e037755. doi: 10.1136/bmjopen-2020-037755 [published Online First: 2020/09/25]
9. Royse CF. The patient's surgical journey and consequences of poor recovery. *Best Pract Res-Clin Anaesth* 2018;32(3-4):253-58. doi: 10.1016/j.bpa.2018.06.001
10. Deiner S, Liu X, Lin H-M, et al. Does postoperative cognitive decline result in new disability after surgery? *Ann Surg* 2021;274(6):e1108-e14.
11. Borchers F, Spies CD, Feinkohl I, et al. Methodology of measuring postoperative cognitive dysfunction: a systematic review. *Br J Anaesth* 2021;126(6):1119-27. doi: 10.1016/j.bja.2021.01.035 [published Online First: 2021/04/07]
12. Jessen F, Amariglio RE, Buckley RF, et al. The characterisation of subjective cognitive decline. *Lancet Neurol* 2020;19(3):271-78. doi: 10.1016/s1474-4422(19)30368-0 [published Online First: 2020/01/21]
13. Curry LA, Krumholz HM, O'Cathain A, et al. Mixed methods in biomedical and health services research. *Circ Cardiovasc Qual Outcomes* 2013;6(1):119-23. doi: 10.1161/circoutcomes.112.967885 [published Online First: 2013/01/17]
14. Shorten A, Smith J. Mixed methods research: expanding the evidence base. *Evid Based Nurs* 2017;20(3):74-75. doi: 10.1136/eb-2017-102699 [published Online First: 2017/06/16]
15. Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. *Kolner Z Soz Sozpsychol* 2017;69(Suppl 2):107-31. doi: 10.1007/s11577-017-0454-1 [published Online First: 2017/10/11]
16. APA. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington, D.C: American Psychiatric Publishing 2013.
17. Nilsson U, Liander K, Rooyackers O, et al. Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study. *BMJ Open* 2019;9(12):6. doi: 10.1136/bmjopen-2019-032650

18. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013;310(20):2191-4. doi: 10.1001/jama.2013.281053 [published Online First: 2013/10/22]
19. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12(3):189-98. doi: 10.1016/0022-3956(75)90026-6 [published Online First: 1975/11/01]
20. Moller JT, Cluitmans P, Rasmussen LS, et al. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* 1998;351(9106):857-61. doi: 10.1016/s0140-6736(97)07382-0 [published Online First: 1998/04/03]
21. Jaensson M, Dahlberg K, Eriksson M, et al. Evaluation of postoperative recovery in day surgery patients using a mobile phone application: a multicentre randomized trial. *Br J Anaesth* 2017;119(5):1030-38. doi: 10.1093/bja/aex331 [published Online First: 2017/10/28]
22. Nilsson U, Dahlberg K, Jaensson M. The Swedish Web Version of the Quality of Recovery Scale Adapted for Use in a Mobile App: Prospective Psychometric Evaluation Study. *JMIR Mhealth Uhealth* 2017;5(12):e188. doi: 10.2196/mhealth.9061 [published Online First: 2017/12/13]
23. Evered L, Silbert B, Scott DA, et al. Recommendations for a new perioperative cognitive impairment nomenclature. *Alzheimer's dement* 2019;15(8):1115-16. doi: https://dx.doi.org/10.1016/j.jalz.2019.05.005
24. Elo S, Kyngäs H. The qualitative content analysis process. *J Adv Nurs* 2008;62(1):107-15. doi: 10.1111/j.1365-2648.2007.04569.x [published Online First: 2008/03/21]
25. Lezak MD, Howieson DB, Bigler ED, et al. Neuropsychological Assessment: OUP USA 2012.
26. Fetters MD, Curry LA, Creswell JW. Achieving integration in mixed methods designs-principles and practices. *Health Serv Res* 2013;48(6 Pt 2):2134-56. doi: 10.1111/1475-6773.12117 [published Online First: 2013/11/28]
27. Wu LM, Tanenbaum ML, Dijkers MP, et al. Cognitive and neurobehavioral symptoms in patients with non-metastatic prostate cancer treated with androgen deprivation therapy or observation: A mixed methods study. *Soc Sci Med* 2016;156:80-9. doi: 10.1016/j.socscimed.2016.03.016 [published Online First: 2016/03/29]
28. Dijkstra JB, Jolles J. Postoperative cognitive dysfunction versus complaints: a discrepancy in long-term findings. *Neuropsychol Rev* 2002;12(1):1-14.
29. Dijkstra JB, Houx PJ, Jolles J. Cognition after major surgery in the elderly: test performance and complaints. *Br J Anaesth* 1999;82(6):867-74.
30. Moller JT, Svennild I, Johannessen NW, et al. Perioperative monitoring with pulse oximetry and late postoperative cognitive dysfunction. *Br J Anaesth* 1993;71(3):340-7. doi: 10.1093/bja/71.3.340 [published Online First: 1993/09/01]
31. Makkar M, Hunter R, Kulkarni A, et al. Postoperative Cognitive Decline in Patients Undergoing Major Gynecologic Oncology Surgery: A Pilot Prospective Study. *J Obstet Gynaecol Can* 2024;46(8):102584. doi: 10.1016/j.jogc.2024.102584 [published Online First: 2024/06/16]
32. Earl Robertson F, Jacova C. A Systematic Review of Subjective Cognitive Characteristics Predictive of Longitudinal Outcomes in Older Adults. *Gerontologist* 2023;63(4):700-16. doi: 10.1093/geront/gnac109 [published Online First: 2022/08/01]
33. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One* 2018;13(4):e0195659. doi: 10.1371/journal.pone.0195659 [published Online First: 2018/04/12]
34. De Cosmo G, Sessa F, Fiorini F, et al. Effect of remifentanil and fentanyl on postoperative cognitive function and cytokines level in elderly patients undergoing major abdominal surgery. *J Clin Anesth* 2016;35:40-46. doi: 10.1016/j.jclinane.2016.07.016 [published Online First: 2016/11/23]

35. Fu C, Lin J, Gong G, et al. Inflammatory markers in postoperative cognitive dysfunction for patients undergoing total hip arthroplasty: a meta-analysis. *Aging Clin Exp Res* 2022;34(2):277-88. doi: https://dx.doi.org/10.1007/s40520-021-01919-7
36. Patel A, Zhang M, Liao G, et al. A Systematic Review and Meta-analysis Examining the Impact of Age on Perioperative Inflammatory Biomarkers. *Anesth Analg* 2022;134(4):751-64. doi: 10.1213/ane.0000000000005832 [published Online First: 2021/12/29]
37. Clemmesen CG, Tavenier J, Andersen O, et al. Methylprednisolone and inflammatory stress response in older people undergoing surgery for hip fracture: a secondary analysis of a randomized controlled trial. *Eur Geriatr Med* 2019;10(6):913-21. doi: 10.1007/s41999-019-00231-y [published Online First: 2019/12/01]
38. Ryan PM, Scherry H, Pierson R, et al. NSAID use in orthopedic surgery: A review of current evidence and clinical practice guidelines. *J Orthop Res* 2024;42(4):707-16. doi: 10.1002/jor.25791 [published Online First: 2024/01/26]
39. Yan Y, Guo TM, Zhu C. Effects of nonsteroidal anti-inflammatory drugs on serum proinflammatory cytokines in the treatment of ankylosing spondylitis. *Biochemistry and Cell Biology* 2018;96(4):450-56. doi: 10.1139/bcb-2017-0267
40. Okinaka Y, Kageyama S, Goto T, et al. Metabolomic profiling of cancer-related fatigue involved in cachexia and chemotherapy. *Sci Rep* 2024;14(1):8329. doi: 10.1038/s41598-024-57747-y [published Online First: 2024/04/10]
41. Fosså A, Smeland KH, Fluge Ø, et al. Metabolic analysis of amino acids and vitamin B6 pathways in lymphoma survivors with cancer related chronic fatigue. *PLoS One* 2020;15(1):e0227384. doi: 10.1371/journal.pone.0227384 [published Online First: 2020/01/11]
42. Christensen MHE, Fadnes DJ, Røst TH, et al. Inflammatory markers, the tryptophan-kynurenine pathway, and vitamin B status after bariatric surgery. *PLoS One* 2018;13(2):e0192169. doi: 10.1371/journal.pone.0192169 [published Online First: 2018/02/06]
43. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of postoperative fatigue. *J Psychosom Res* 2004;57(3):317-26. doi: 10.1016/s0022-3999(03)00615-9 [published Online First: 2004/10/28]
44. Cohen CL, Atkins KJ, Evered LA, et al. Examining Subjective Psychological Experiences of Postoperative Delirium in Older Cardiac Surgery Patients. *Anesthesia & Analgesia* 2022;06:06. doi: https://dx.doi.org/10.1213/ANE.0000000000006226
45. Toba MN, Malkinson TS, Howells H, et al. Same, Same but Different? A Multi-Method Review of the Processes Underlying Executive Control. *Neuropsychol Rev* 2023 doi: 10.1007/s11065-023-09577-4 [published Online First: 2023/03/27]
46. Karlsson Å, Olofsson B, Stenvall M, et al. Older adults' perspectives on rehabilitation and recovery one year after a hip fracture - a qualitative study. *BMC Geriatr* 2022;22(1):423. doi: 10.1186/s12877-022-03119-y [published Online First: 2022/05/14]
47. Li L, Dohan D, Smith AK, et al. 'It was a great brain, and I miss it': lay perspectives on postoperative cognitive dysfunction. *Br J Anaesth* 2023;130(5):567-72. doi: 10.1016/j.bja.2023.02.003 [published Online First: 2023/03/04]
48. Nilsson U, Dahlberg K, Jaensson M. Low Preoperative Mental and Physical Health is Associated with Poorer Postoperative Recovery in Patients Undergoing Day Surgery: A Secondary Analysis from a Randomized Controlled Study. *World J Surg* 2019;43(8):1949-56. doi: 10.1007/s00268-019-04995-z [published Online First: 2019/04/03]
49. Jaensson M, Dahlberg K, Nilsson U. Factors influencing day surgery patients' quality of postoperative recovery and satisfaction with recovery: a narrative review. *Perioper Med (Lond)* 2019;8:3. doi: 10.1186/s13741-019-0115-1 [published Online First: 2019/05/30]
50. Ditton E, Johnson S, Hodyl N, et al. Improving Patient Outcomes Following Total Knee Arthroplasty: Identifying Rehabilitation Pathways Based on Modifiable Psychological Risk and Resilience Factors. *Front Psychol* 2020;11:1061. doi: 10.3389/fpsyg.2020.01061 [published Online First: 2020/07/17]

51. Mogic L, Rutter EC, Tyas SL, et al. Functional social support and cognitive function in middle- and older-aged adults: a systematic review of cross-sectional and cohort studies. *Syst Rev* 2023;12(1):86. doi: 10.1186/s13643-023-02251-z [published Online First: 2023/05/22]
52. Reza T, Grezenko H, Barker C, et al. Emotional Stress and Immune Response in Surgery: A Psychoneuroimmunological Perspective. *Cureus* 2023;15(11):e48727. doi: 10.7759/cureus.48727 [published Online First: 2023/12/14]

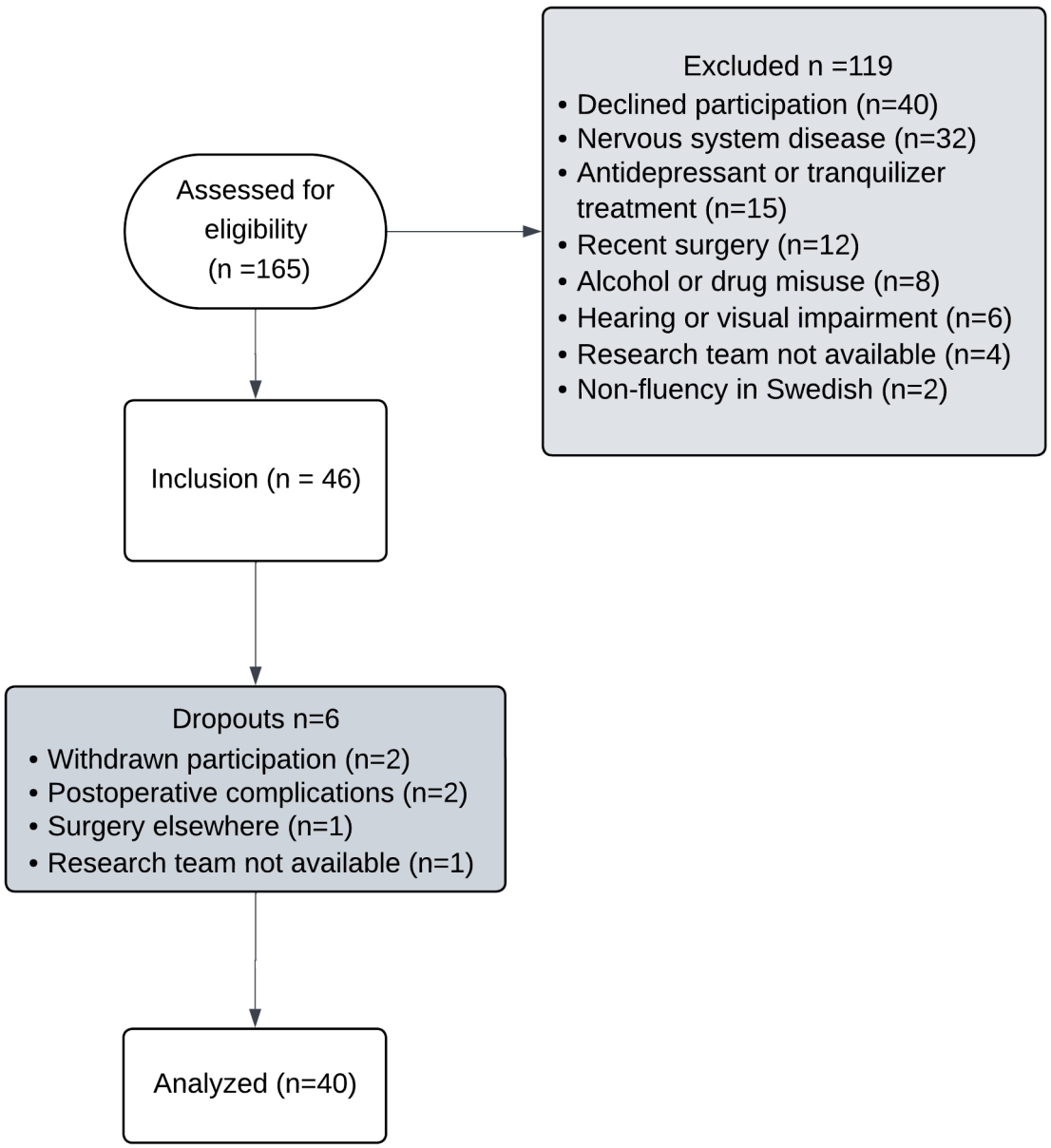

Figure 1: Flow chart of participans

BMJ Open

Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study

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To cite: Nilsson U, Liander K, Rooyackers O, *et al*. Patients' experiences of early postoperative cognition and its relation to cognitive decline and inflammatory responses: a protocol for a mixed-methods study. *BMJ Open* 2019;**9**:e032650. doi:10.1136/bmjopen-2019-032650

▶ Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2019-032650).

Received 05 July 2019
Revised 21 November 2019
Accepted 22 November 2019

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ABSTRACT

Introduction In the early weeks after surgery, patients may experience cognitive changes and impaired memory and concentration—changes commonly referred to as postoperative cognitive decline. It is often the patient and/or a relative that initially detects a change in cognitive capacity after surgery, typically when resuming daily activities. We lack information about how patients experience early postoperative cognition (*delayed neurocognitive recovery*) and if these experiences can be reflected in biochemical pattern of inflammatory signalling molecules, cognitive function as well as on quality of postoperative recovery.

Methods and analysis The study has a mixed-methods design that is integration of qualitative and quantitative data within a single investigation. Participants included will be patients aged ≥60 years that are undergoing major elective joint replacement surgery (n=40) and their relative. Patient's experience of his/her early cognition will be captured by interviews on postoperative day 13–16 during the follow-up visit. A relative will also be interviewed on the same day or the day after. Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction test battery. Symptoms/discomfort will be measured preoperatively and postoperatively (on postoperative day 1 and 2 and at the follow-up visit day 13–16) by the Swedish version of Quality of Recovery and by a visual analogue scale assessing pain intensity. Biomarkers will also be collected at the same time points. The findings from the interviews will be sorted out depending on group stratification (no delayed neurocognitive recovery and delayed neurocognitive recovery). The qualitative and quantitative findings will be compared to seek for similarities and differences.

Ethics and dissemination The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments. Results from this study will be disseminated in peer-reviewed journals, scientific conferences and in social media.

Strengths and limitations of this study

- ▶ A mixed-methods study comparing patients' experiences of early postoperative cognition with patterns in biochemical pattern of inflammatory signalling molecules, cognitive function assessed with validated neuropsychological tests as well as on quality of postoperative recovery.
- ▶ Patients' own experiences of early postoperative cognition including their relative's view have never been reported earlier.
- ▶ This study includes a small sample of patients and is conducted in Sweden, and may not be generalisable to other contexts.

INTRODUCTION

Postoperative neurocognitive decline (POCD, previously termed postoperative cognitive dysfunction) is one of the the most common complications after otherwise uneventful surgery and affects multiple cognitive domains such as memory, executive functions, information processing speed and attention[1–5] with subsequently impaired day-to-day memory, language skills, attention and learning compared with levels demonstrated preoperatively.[6] Postoperative cognitive decline is diagnosed up to 30 days postoperatively (*delayed neurocognitive recovery*)[7] and is a subtler deterioration in cognition, as it is not characterised by obvious clinical symptoms such as a change in the level of consciousness.[8] With advanced age as the primary risk factor for neurocognitive decline,[2 4 5 8–10] the incidence of cognitive dysfunction in elderly patients 1 week after surgery is approximately 25%[2 9–11] and remains at 10% at 3 months.[2 9 10] Intraoperative factors have been hypothesised as playing a role in the occurrence of POCD. Yet, choice of anaesthesia (general vs regional) has not been found to influence

development of POCD[8 12 13] as well as the choice of anaesthetic agent,[14] depth of anaesthesia[15] and intraoperative hypotension.[16]

While the mechanism behind postoperative neurocognitive disorders are not fully uncovered, there is a growing body of evidence that surgery-induced inflammation spread systemically via blood-borne immune cells and cytokines to the brain via a disrupted blood-brain barrier, resulting a transient neuroinflammation with impaired cognitive processing.[17 18] It has been reported an inflammatory response to surgical procedure has significant involvement in the POCD development.[11] This postoperative neuroinflammatory reaction can be altered by multiple factors within the perioperative period such as pain, sleep disturbances and prolonged infection.[6]

Because clinical evaluation of the brain is not a routine part of preoperative evaluation[19] and the discrete nature of cognitive disorders, it is often the patient and/or a relative who in the first instance detects a change in cognitive capacity after surgery, typically when resuming daily activities.[5] It has also been reported that elderly patients are 'never the same' after surgery.[12] Evidence suggests that neurocognitive decline can act as a precursor of significant functional impairment following surgery; patients developing neurocognitive decline leave the labour market early and are more dependent on social transfer payments.[20] Neurocognitive disorders are, furthermore, associated with increased mortality[3 20] and with prolonged hospitalisation.[4] Evered *et al* proclaim that perioperative cognition has become largely a research area rather than a clinical state meaning that subjective aspects are rarely sought or reported as well as capacity for activities of daily living is overlooked. Therefore, a subjective report from the patient is an essential element of diagnosing a perioperative neurocognitive decline.[7]

Aim

The aim of present study is therefore to explore patients' experiences of their early postoperative cognition after major orthopaedic surgery in relation to postoperative cognitive function assessed with validated neuropsychological tests, inflammatory signalling molecules and quality of postoperative recovery as well as to describe the relative's view of early postoperative cognition.

METHODS AND ANALYSIS

Study design

A mixed-methods study that is inductive concurrent design where the core component is qualitative and the supplemental component is quantitative with integration of qualitative and quantitative data within a single investigation[21 22] will be undertaken to address the research questions. Study recruitment started in October 2019 and is planned to end in April 2020.

Participants

Patients

Participants included will be patients undergoing major elective joint replacement surgery (n=40) at a university hospital in Sweden. The sample size is based on the mixed-methods study design and the incidence of early cognitive decline at 1–2 weeks postoperatively of 17%–25%.[2 23] However, unpublished research with new reference values indicates that the incidence is underestimated, and instead up to 50% can suffer from POCD.

Exclusion criteria: a score on the Mini-Mental State Examination (MMSE) at screening of ≤22, that is, suspected dementia[24]; <60 years of age; suffering from a nervous system disease; taking tranquillisers or antidepressants; underwent a surgical procedure in the previous 6 months; inability to read and speak Swedish or suffering from a severe visual or auditory disorder, alcoholism or drug dependence.

Relatives

One close relative (spouse or children with age ≥18 years) per patient will be asked to participate. Inclusion criteria for the relatives included identifying themselves as being a relative whom the patient included in the study and being able to take part in an interview in Swedish. The patient decides which relative should be asked. If the relative does not accept to be included, the patient will not be excluded.

Recruitment

One of the researchers will, during their preoperative anaesthesia consultation, provide oral and written information about the study. The details of the study and its potential benefits as well as risks will be explained thoroughly to the patient. If the patient agrees to participation in the study, they will undergo the MMSE screening. Values >22 indicated that the patient is eligible to participate (figure 1).

Qualitative data

Interviews

The patients and their relative will be interviewed separately. The opening question to the patients is: *"How do you yourself experience the time after the operation compared to before?"* Opening question to the relative: *"How would you describe your relative regarding being as they used to be, being themselves, before the operation compared to the time after surgery"*. Probing questions were asked such as *"What do you mean?"* and *"How would you describe that?"* The informants will be encouraged to speak freely about the experience. An interview guide will be used to ensure covering issues such as cognition, memory loss, attention, mood and daily activity.

Quantitative data

Cognitive testing

Cognitive function will be measured preoperatively and on postoperative day 13–16 using the International Study Group of Postoperative Cognitive Dysfunction (ISPOCD)

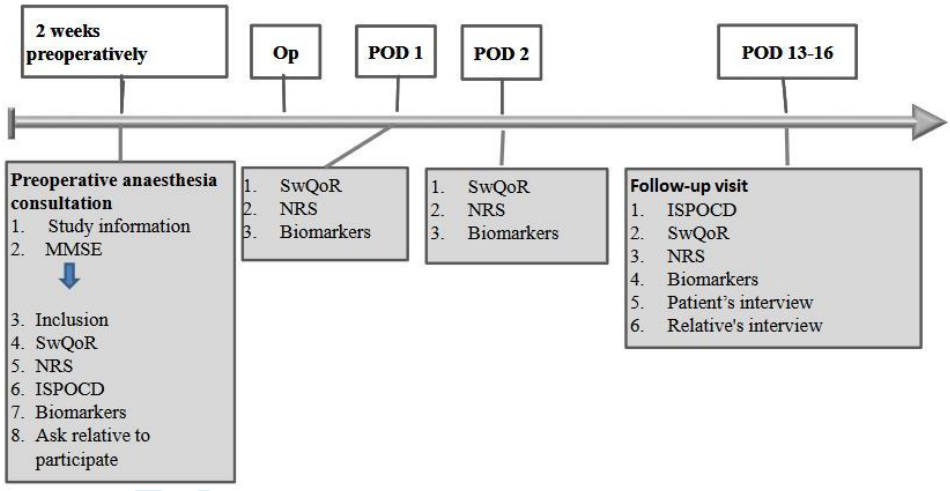

Figure 1 Overview of the research process. ISPOCD, International Study Group of Postoperative Cognitive Dysfunction; MMSE, Mini-Mental State Examination; NRS, numerical rating scale; POD, postoperative day; SwQoR, Swedish version of Quality of Recovery.

neuropsychological test battery. The ISPOCD battery assesses cognitive performance using four different tests, providing seven variables for analysis, including Visual Verbal Learning Test, the Concept Shifting Test, the Stroop Colour-Word Test, the Letter-Digit Coding Test[2] and has been validated in the perioperative setting for two decades.[6] The tests will be administered in the same sequence at each test session by the same researcher following a standardised instruction manual in order to ensure as uniform a test situation as possible. The tests will be carried out in quiet rooms and only the patient and a researcher (KL) will be present.

Blood-borne biomarkers

Inflammatory signalling molecules such as C reactive protein, interleukin 1-beta, interleukin-6, interleukin-10, High Mobility Group Box 1 (HMGB-1) and fractalkine will be measured preoperatively and postoperatively. Venous blood samples (20 mL whole blood) will be drawn from an intravenous cannula. Blood will be centrifuged and plasma stored at −80°C until further analysed.

Quality of recovery

The patients' quality of recovery will be measured by the Swedish version of Quality of Recovery (SwQoR), which measures 24 different items related to symptoms/discomfort that appear postoperatively, such as pain, anxiety, sleep difficulties, dizziness, fatigue, returning to work or usual home activities. The items are rated on 11-point numerical scales ranging from 0, 'none of the time', to 10, 'all of the time'. Reliability and validity tests have provided evidence that it is appropriate to use SwQoR in patients undergoing surgery.[25]

Pain intensity

Pain intensity will be measured using a numerical rating scale (NRS) from 0=no pain to 10=maximum possible pain. The NRS has been tested for reliability and validity in a Swedish population.[26]

Demographic and perioperative data

These include: age, sex, MMSE score, comorbidities, American Society of Anaesthesiologists classification, aesthetic technique and duration, duration of the procedure, blood loss (mL), blood transfusion (mL), use of analgesics during hospitalisation and at home until the follow-up visit, postoperative complications and length of stay.

Procedure

Preoperative data collection

If the patient chooses to participate in the study, they will undergo the cognitive test preoperatively. The test will be performed in an undisturbed room where only the patient and researchers will be present. The tests are expected to take about 20 min. Blood-borne biomarkers will be collected and SwQoR and pain intensity questions will be measured after the cognitive testing is completed (table 1 and figure 1). The day and time of day for preoperative data collection will be documented.

Postoperative data collection

The cognitive test and the interview with the patients will take place on postoperative day 13–16 during the patient's follow-up visit. After the cognitive test is completed, SwQoR and biomarkers will be measured. The patient's relatives will be interviewed separately on the same day or the day after and by the same researcher (KL). All cognitive tests will be performed by one of the researchers from the research group (KL), with education and experience of performing the test. SwQoR, pain intensity and blood-borne biomarkers will be measured postoperative day 1–3, the same time of day ±2 hours and on day 13–16 during patient's follow-up visit. The day and time of day for sampling biomarkers at the follow-up visit will be documented. A research nurse at the Clinical Research Unit at the University Hospital will collect all biomarkers (table 1 and figure 1).

Table 1 Outcome measures

Outcome		Preoperative	POD 1	POD 2	POD 13–16
Cognitive test	ISPOCD battery	X			X
Neuroinflammatory reaction	Blood-borne biomarkers	X	X	X	X
Postoperative recovery	Swedish version of Quality of Recovery questionnaire	X	X	X	X
Pain intensity	Numerical rating scale	X	X	X	X
Experiences of postoperative cognition	Interviews with patients and relatives				X

ISPOCD, the International Study Group of Postoperative Cognitive Dysfunction; POD, postoperative day.

Data analysis

Qualitative data analysis

All interviews will be transcribed verbatim and analysed in line with an inductive thematic analysis.[27] In the first step, all interviews will be read through, patients and relatives separately, and expressions concerning the experienced postoperative cognitive decline will be marked. At the same time, initial reflections on the data will be noted. In the second step, the marked expressions will be coded into a condensed, semantic description of the experiences expressed. Third, themes will be identified, based on sorting the codes and initial reflections. In this step, relations between and levels of the themes will also be mapped. In step four, a review of the themes will be conducted, in which all codes included in a theme are considered, following which the whole analysis is considered in relation to the initial reflections and original texts. Thereafter, all themes and subthemes will be named. The findings from patients and relatives will be presented separately as well as being compared to seek for similarities and differences, and will be highlighted. Also, individual similarities and differences within the couples will be presented. The data analysis will be blinded to the findings from the biomarkers, cognitive tests, SwQoR and pain in order to not be influenced. The analysis will be performed in Swedish and thereafter be translated into English.

Quantitative data analysis

Changes in cognitive performance will be calculated for each of seven test variables and corrected for practice effects and variability using data from a historical age-matched control group that has undergone testing using the same battery and with the same intervals.[2] To quantify the change from preoperative test to the postoperative tests scores, separate and composite z-scores will be calculated on the basis of the seven cognitive test results and compared using Mann-Whitney U rank sum test.

To analyse differences in biomarkers within patients and between patients, χ^2 or Student's t-test will be used. To analyse differences within patients and between patients in cognitive performance and postoperative recovery, Mann-Whitney U rank sum tests will be used. For statistical analyses, IBM SPSS statistics V.24 for Windows will be used (IBM, Armonk, New York, USA). A p value of <0.05 will be considered to be statistically significant in all analyses.

Descriptive statistics of demographic and perioperative data will be presented by number, percentage and mean (SD) or min-max, as appropriate. Depending on the results from the cognitive tests and biomarkers, the patients will be stratified on the basis of their postoperative composite cognitive z-score result into two groups: no delayed neurocognitive recovery corresponding to a composite z-score <1 or delayed neurocognitive recovery with composite z-score ≥1.0.[2] Patient characteristics will be compared, between these two groups, using Fisher's exact test for categorical outcomes and t-tests or the Wilcoxon rank-sum test for continuous variables, as appropriate. A difference will be considered if any of these characteristics between the two groups has a p value of <0.05.

The analytical point of integration

The qualitative and quantitative findings will be brought together to look for similarities, that is, whether the qualitative and the quantitative findings yield convergent results (*triangulation*)[22] or if they are diverged. Thereafter, the findings from the interviews, both patients and relatives, will be sorted out depending on group stratification (no delayed neurocognitive recovery or delayed neurocognitive recovery). The qualitative and quantitative findings will then be compared to seek for similarities and differences. All patients will be included in the mixed data analysis even though they have an improvement in z-score, SwQoR or biomarkers.

Dissemination

The study results will be disseminated through peer-reviewed publications and conference presentations to the scientific community and social media.

Patient and public involvement

Patients were not involved in the design of the study and will not be involved in the recruitment of participants. The results of the project will be disseminated through scientific papers.

DISCUSSION

Knowledge can be obtained both by understanding and explaining a phenomenon of interest, which is the reason why a mixed-methods design including both qualitative and quantitative data will be used. By merging qualitative and quantitative data, we will look for confirmation, expansion and discordance in the different datasets. Confirmation occurs when the data confirm each other, that is, that the results from the qualitative and quantitative analyses confirm the results in the respective outcome. The data can also expand, that is, when the outcomes diverge and expand or complement the results from the qualitative and quantitative findings. Discordance occurs when the results from the different data conflict, or disagree, with each other.[21 22] When results from the quantitative and qualitative study do not match completely, this enhances the robustness of the study by illustrating the complexity of the problem studied.[28] In this study, the quantitative data include both objective (biomarkers and cognitive testing) and subjective (SwQoR and postoperative pain) outcomes and the qualitative data include both the patient's and the relative's view.

POCD is a major neurological adverse outcome following major surgery[5 6 29] with age as one of the major risk factors.[2 4] Cognitive assessment in order to capture POCD is not a routine part of clinical practice, and nor do we have any evidence for patients' and their relatives' own experience of suffering from POCD and whether there is a relation between objective and subjective outcomes of it. The knowledge from the present project as well as earlier evidence from studies assessing POCD will create a base in developing a gamified version of the traditional pen-and-paper cognitive assessment tools, in order to start assessing POCD in an easy and secure way in clinical practice. Until this is done, the results from the present project will generate evidence for clinical practice to detect patients with POCD by identifying signs and symptoms that patients and their relatives themselves describe when suffering from POCD.

ETHICAL CONSIDERATIONS

It is recognised that the study protocol involves cognitive tests that may display pre-existing and previously unknown cognitive impairment.[30] Detailed information about the extent and duration of cognitive tests, including possible outcomes, will be carefully explained and the patient and the relative can refuse to participate on the basis of this information. In addition, participants will be informed that the study is voluntary and that the data would be treated with confidentiality. They will also be informed that they can terminate their participation at any time. Written informed consent will be obtained from the participants after they have received written and verbal information about the study, including the purpose and procedures, the voluntariness of participation and the option to withdraw at any time. They will also be guaranteed confidentiality and secure data storage. We will follow good clinical practice in the conduct of clinical trials.

The study follows the recommendations of the World Medical Association General Assembly that include principles considering the prospective registration and the public disclosure of study results to be ethical obligations, as follows: '*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject*' and '*Negative and inconclusive as well as positive results should be published or otherwise made publicly available*'. All researchers will follow the Uniform Requirements for Manuscripts.[31]

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Contributors UN has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version. KL has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version. OR has contributed to the planning of the biomarkers and the preparation of the manuscript and approved of the final version. LIE has contributed to the planning of the study, study design, the preparation of the manuscript and approved of the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The project has been approved by the Swedish Ethical Review Authority (2019–02968) and will follow the principles outlined in the 1964 Helsinki Declaration and its later amendments.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Krenk L, Rasmussen LS, Kehlet H. New insights into the pathophysiology of postoperative cognitive dysfunction. *Acta Anaesthesiol Scand* 2010;54:951–6.
2 Moller JT, Cluitmans P, Rasmussen LS, *et al*. Long-Term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *The Lancet* 1998;351:857–61.
3 Monk TG, Weldon BC, Garvan CW, *et al*. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008;108:18–30.
4 Newman MF, Kirchner JL, Phillips-Bute B, *et al*. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *N Engl J Med* 2001;344:395–402.
5 Rasmussen LS. Postoperative cognitive dysfunction: incidence and prevention. *Best Pract Res Clin Anaesthesiol* 2006;20:315–30.
6 Funder KS, Steinmetz J, Care C. Post-Operative cognitive dysfunction – lessons from the ISPOCD studies. *Trends in Anaesthesia and Critical Care* 2012;2:94–7.

7 Evered L, Silbert B, Knopman DS, *et al*. Recommendations for the nomenclature of cognitive change associated with anaesthesia and Surgery-2018. *Anesthesiology* 2018;129:872–9.
8 Steinmetz J, Rasmussen LS. Postoperative confusion. *Minerva Anestesiol* 2018;84:157–8.
9 Ballard C, Jones E, Gauge N, *et al*. Optimised anaesthesia to reduce post operative cognitive decline (POCD) in older patients undergoing elective surgery, a randomised controlled trial. *PLoS One* 2012;7:e37410.
10 Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly - what are the differences? *Minerva Anestesiol* 2011;77:742–9.
11 Glumac S, Kardum G, Sodic L, *et al*. Effects of dexamethasone on early cognitive decline after cardiac surgery: a randomised controlled trial. *Eur J Anaesthesiol* 2017;34:776–84.
12 Deiner S, Silverstein JH. Postoperative delirium and cognitive dysfunction. *Br J Anaesth* 2009;103 Suppl 1:i41–6.
13 Wu CL, Hsu W, Richman JM, *et al*. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. *Reg Anesth Pain Med* 2004;29:257–68.
14 Deiner S, Luo X, Silverstein JH, *et al*. Can intraoperative processed EEG predict postoperative cognitive dysfunction in the elderly? *Clin Ther* 2015;37:2700–5.
15 Steinmetz J, Funder KS, Dahl BT, *et al*. Depth of anaesthesia and post-operative cognitive dysfunction. *Acta Anaesthesiol Scand* 2010;54:162–8.
16 Langer T, Santini A, Zadek F, *et al*. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. *J Clin Anesth* 2019;52:111–8.
17 Forsberg A, Cervenka S, Jonsson Fagerlund M, *et al*. The immune response of the human brain to abdominal surgery. *Ann Neurol* 2017;81:572–82.
18 Terrando N, Eriksson LI, Ryu JK, Kyu Ryu J, *et al*. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol* 2011;70:986–95.
19 Sauër A-M, Kalkman C, van Dijk D. Postoperative cognitive decline. *J Anesth* 2009;23:256–9.
20 Steinmetz J, Christensen KB, Lund T, *et al*. Long-Term consequences of postoperative cognitive dysfunction. *Anesthesiology* 2009;110:548–55.
21 Creswell JW. Controversies in mixed methods research. The SAGE Handbook of qualitative research 2011;4:269–84.
22 Schoonenboom J, Johnson RB. How to Construct a Mixed Methods Research Design. *Köln Z Soziol* 2017;69:107–31.
23 Silbert B, Evered L, Scott DA, *et al*. Preexisting cognitive impairment is associated with postoperative cognitive dysfunction after hip joint replacement surgery. *Anesthesiology* 2015;122:1224–34.
24 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
25 Nilsson U, Dahlberg K, Jaensson M. The Swedish web version of the quality of recovery scale adapted for use in a mobile APP: prospective psychometric evaluation study. *JMIR Mhealth Uhealth* 2017;5:(e188).
26 Lundeberg T, Lund I, Dahlin L, *et al*. Reliability and responsiveness of three different pain assessments. *J Rehabil Med* 2001;33:279–83.
27 Braun V, Clarke V. Using thematic analysis in psychology. *Qual Res Psychol* 2006;3:77–101.
28 Moffatt S, White M, Mackintosh J, *et al*. Using quantitative and qualitative data in health services research - what happens when mixed method findings conflict? [ISRCTN61522618]. *BMC Health Serv Res* 2006;6:28.
29 Krenk L, Kehlet H, Bæk Hansen T, *et al*. Cognitive dysfunction after fast-track hip and knee replacement. *Anesthesia & Analgesia* 2014;118:1034–40.
30 Association WM. World Medical association Declaration of Helsinki. ethical principles for medical research involving human subjects. *Bull World Health Organ* 2001;79.
31 Barron JP. The uniform requirements for manuscripts submitted to biomedical journals recommended by the International Committee of medical Journal editors. *Chest* 2006;129:1098–9.

Supplementary material

1. Procedure of content analysis

Categories	Subcategories	Codes	Quotes
Executive Functions	Problem-solving	Performance awareness	And I have learned to walk, so that it works. But it was an effort I didn't think I would have to make. But it was the first time in these 50 years that I feel strained (P01)
			So you learn a lot of tricks. You position yourself in a corner. Leverage against the back, and then you stand on the leg you're allowed to put weight on. Yes, and then you manage some things with the coffee maker (P43)
	Emotional regulation	Feeling grumpy and snapping	I've been a bit grumpy, I guess. I don't need to hide that. But no one has taken offense. I've tried to be kind and nice, but sometimes you just snap a bit (P10).
		Having a short fuse	So, I have a pretty short fuse, and I lose patience when things don't go smoothly... like when I can't put on my pants and stuff, so then I get angry. And then it might happen that a crutch ends up in the wall or something (P31)
	Energization	Avoiding initiatives and others	Yeah, I've mostly been lying in bed. That's what I've done. And I've been served food and everything, I haven't had to do anything. I have my grandchildren living with me, so he has helped a lot (P06).
		Not thorough as before and delaying action	I notice that's not like me. I am very thorough about everything. But now, there are things everywhere, and, by the way, it's hard to pick up. But I think, well, I'll do that later. But I haven't done it yet (P08).
	Fatigue	Mental fatigue	But administrative tasks are no problem, but sitting down to write assignments, I don't have the concentration for that. I get too tired (P31).
		Motoric fatigue	

			The only thing I've managed is to go to the bathroom and take care of my needs and... yes, brush my teeth and things like that. // I can handle such tasks, but nothing else. I don't have the energy for it, I'm too tired. // I couldn't even dress myself at first. My husband had to help me get dressed, you know (P06). I am tired, physically ... if I go out and walk, as I have tried to do for the last three days…then I am quite tired afterwards…Yes, it's time to lie down. And then I'm not really fit for fight ... I'm don't have much energy for the rest of the day. (P31)
Attention and memory	Subjective memory decline	Doubting memory function	But, you know, it's just that you start to think that you're not sure when you yourself stop noticing that you forget things (P05).
		Memory decline	Yes, I feel like I've had a really poor memory for a long time now. Because I've been anxious about the surgery, and that affects concentration a bit. And I haven't been feeling very well before either (P07).
	Family concern of memory decline	Family member pointing out memory decline	If I have experienced some memory loss, it's possible, it's possible. Because our children said, 'Dad, you won't remember this. It was like this' (P01).
	Sustained attention	Losing the thread	Now it can be distracting around as well, I mean you can... What should I say? You lose the thread. If we have a study that we have read, a large section, so... //Now I haven't had the energy to participate and haven't had the energy to read up. I can't go through everything now, no. I don't do that (P06).
		Feeling absent-minded	So right now, I can read and read and read, and still, I find myself stuck on the same sentence, and then and then it's just as good to leave it// Uhm, concentration, I can't concentrate properly (P10). Today, I showered with the hearing aids on. It wasn't good (P01).

		Lack of focus	These last few days, I have found it challenging. I have these magazines that I subscribe to, that I receive. So I haven't had the energy to read them properly. I haven't been able to focus on it (P39).
Psychological factors	Sense of agency	Lack of agency	But it's connected to the fact that I'm the kind of person who has a need for control, too, so that... And you don't have that when you surrender yourself to healthcare. (P05)
		Wanting to manage things independently	Sometimes it's my dear wife... I become more easily irritated, perhaps. It has to do with her trying to be overly protective and fetch everything for me, and I think to myself, "I can handle this on my own," and then I get slightly annoyed at trivial things that are not relevant (P03)
	Powerlessness	Being dependant on others	…To 110%. I don't want to be dependent. Absolutely. //... Yes, I become disheartened and a little angry, and... What should I say? //... Just this being dependent, it's... Yes, I want to do everything myself if I may say so. Control my day, or control and manage and so on (P08)
			And the thing about being dependent on other people and... you don't want to bother people, even if they're your own sons, it feels like 'God, how annoying I am.' And then I get in a bad mood (P19).
	Physical limitations	Feeling low	I feel a bit depressed because I can't do anything, and not fix anything, not fetch anything, not pick up anything (P08)
			I have a different way, a different temperament. I don't recognize myself. I am sometimes sad, and that's not something I used to be (P46).
	Future perspectives	Brighter outlook	

	I feel much more positive now than right after the surgery, as I sense that the pain is heading in the right direction, and the mobility in the operated leg also feels much better, in that way. So, I feel that I am regaining a bit more zest for life compared to before the surgery (P03).
	I think maybe I was grumpier before the surgery than after, because now it's done. And now, well, theoretically at least, it can't get worse. Now it's just going to get better (P12)

Supplementary material 2
Interview guide

Open question to patients, encouraging them to speak freely about their experiences regarding memory, concentration, and recovery after hip replacement surgery.

- How do you perceive yourself from the time you were cared for in the recovery ward until now?
- How would you describe yourself since you underwent your hip replacement surgery?
- Do you recognize yourself after your hip replacement surgery? In what way? Please describe what you mean.
- How is your memory after the surgery compared to before? When and how did you notice any changes? Can you provide an example?
- Do you experience any changes in your concentration and attention? Can you elaborate on what you mean? Would you like to give an example or describe a situation?
- Have you experienced or do you experience changes in your mood after the surgery? Feel free to elaborate on your answer.
- Can you describe your sleep before and after the surgery? If it has changed, what do you think it might be due to? In what way is your sleep changed?
- Do you feel completely restored to your usual self, regarding your cognitive abilities after your surgery? If not, describe freely in what way and how. Can you describe the process?
- How do you perceive your ability to initiate your daily activities? Can you provide examples and describe it?
- How are your energy levels?