Chronic Post-surgical Pain, Postoperative Cognitive Dysfunction and Resilience in older people undergoing elective knee or hip surgery: a mixed method project to explore associations and underlying mechanisms. The **ArthroCaP** study

Short title (max 25 characters): CPSP, POCD and Resilience

Protocol Version 3.0
July 25, 2022

Table of Contents

1. BACKGROUND AND RATIONALE

Surgery has been associated with short and long-term changes in cognition (postoperative cognitive dysfunction, POCD).[1 2] The literature shows that most often patients show POCD during the first 1-3 months after surgery, and then recover.[3] However, in the recently published NeuroVISION study, up to 30% of 65 years old or older people undergoing different types of noncardiac surgery presented a decline of ≥2 points in their Montreal Cognitive Assessment (MoCA) score at 1 year after surgery compared to prior to surgery.[4] A ≥2 points in MoCA score has been shown to correspond to cognitive decline based on formal neuropsychological testing and to be of clinical significance.[5 6] The risk factors and determinants of POCD are poorly understood.[7]

Chronic pain has been associated with cognitive dysfunction, in particular memory and concentration deficits.[8] The existing literature on chronic pain in general supports the hypothesis of a bidirectional interaction between pain and cognitive processing.[8] However, in a longitudinal community-based study, a history of persistent pain (of any origin) at baseline was associated with memory decline, and even dementia, over 10 years of follow-up.[9] We hypothesize that a similar association might exist between post-surgical pain, and in particular chronic post-surgical pain (CPSP) and POCD (**objective 1**). A surgical population including older ages and with an expected high prevalence of CPSP, like patients undergoing total knee and hip replacement,[10] seems a suitable population to evaluate this association. In this population, up to 23% of hip replacement and 34% of knee replacement surgery patients experience long term pain after surgery.[11] The long-term need of analgesic therapy, and in particular, the chronic use of opioids in patients with CPSP, could also play an independent role in mediating the association between CPSP and cognitive changes. Overall, the existing literature on the association between CPSP and POCD, including the role of long-term opioid use, is very scanty and controversial.[11-13]

The presence of pain, and in particular joint pain, can significantly interfere with mobility, and an impaired physical performance can eventually affect the cognitive performance.[14] The Self-Administered Patient Satisfaction (SAPS) Scale is used as a more comprehensive measure of patient recovery after surgery, since it includes the overall satisfaction with surgery, self-reported extent of pain relief, and ability to perform home or yard work, and recreational activities.[15] Therefore it is also plausible to hypothesize an association of patient satisfaction (as measured by the SAPS) after surgery with long-term cognitive changes (**objective 1**).

Mechanisms with which postoperative pain and satisfaction could affect postoperative cognitive changes are unclear. One interesting hypothesis is that pain and satisfaction might interact with cognitive abilities through neurogenesis interference (**objective 2.a**).[8] This would be similar to what is observed in depression.[16 17] Numerous studies in animals have linked depression with hippocampal-reduced neurogenesis. In rodents, reduced neurogenesis is both a consequence of chronic stress exposure, and a vulnerability that predisposes animals to develop depressive symptoms when later subjected to stress.[18] In the absence of a non-invasive measure of neurogenesis in humans, correlational evidence in human studies has identified several high interference memory tests (like the Mnemonic Similarity Test [MST]) as putatively neurogenesis-sensitive, because they are similarly impacted by factors that alter neurogenesis levels in rodents.[19 20] In humans, deficits on the MST are associated with elevated scores on scales of

stress, depression and binge drinking, and with increased age, while several weeks of high intensity exercise improve MST scores.[21] [22] Even if 30% of the NeuroVISION participants presented a decline of ≥2 points in their Montreal Cognitive Assessment (MoCA) score at 1 year, many participants experienced no changes or an improvement in their MoCA scores. To assess the role of neurogenesis in the association between CPSP and POCD, we can assess the correlation between changes in pain scores (and incidence of CPSP) with the MST, and separately with other cognitive/neuropsychological testing. According to the neurogenesis theory, as demonstrated in depressed patients recovering from their depressive state,[17] we might see improved MST scores in patients who experience a postoperative improvement in their pain while still showing a postoperative decline in other cognitive domains/tests; and *vice versa*, patients with CPSP might show worsened MST scores, without showing significant changes in other cognitive tests/domains. Neurotrophic factors support the survival and function of hippocampal cells. Neurotrophic like the brain-derived neurotrophic factor (BDNF) and the insulin-like growth factor-1 (IGF-1) have been shown to enhance the association between higher aerobic fitness and better memory performance.[23] Conversely, a reduction in neurotrophic factors might mediate the interaction of pain, reduced mobility and satisfaction, with cognition (**objective 2.b**).

The Somatic Preoccupation and Coping (SPOC) questionnaire has been developed to measure postoperative patients' coping abilities and recovery expectations in trauma orthopedic surgery.[24] The SPOC has been showed to predict 1-year pain persistence and functional recovery, in patients after extremity fractures, independently of age.[25] It is possible that coping abilities and expectation are also playing a role in recovery from elective orthopedic surgery. However, this has been never confirmed in the TKA context. Moreover, the SPOC has been validated and tested in overall younger populations. A possible decline in cognitive performance the first months after surgery, that especially older surgical populations might experience, has never been taken into account in previous studies measuring SPOC 4-6 weeks after surgery. In fact, coping strategies and expectations might also be affected by cognitive abilities, and *vice versa* (**objective 3**). Although potentially very useful in clinical practice for a quantitative measurement of patient coping abilities and expectations, the SPOC can give only a partial understanding of patient resilience, i.e. how people live the experience of surgery, how and why they make choices about, and engage (or not) in, a surgical treatment for their condition, across different ages and comorbidities, in particular when suffering from a condition that interfere with their function (**objective 4**).

With this as background and rationale, we propose to undertake the ArthroCaP study, i.e., a mixed-method study with the following objectives.

2. OBJECTIVES

The overarching objective of the ArthroCaP study is to explore the interplay between postoperative pain and self-reported recovery (i.e. satisfaction), coping abilities/expectations about surgery, and postoperative COGNITIVE trajectories in ≥50 years old people undergoing elective total knee arthroplasty (TKA) or total hip arthroplasty (THA).

The specific objectives of the ArthroCaP study are:

1. **to explore the association of CPSP, long-term opioid use, and a multi-domain measure of patient satisfaction, with POCD, measured as changes over time of the performance at the Montreal Cognitive Assessment (MoCA) score, and at additional neuropsychological testing.**
2. **to explore whether postoperative cognitive changes are associated with changes in neurogenesis correlates (a) and in neurotrophic factors levels (b), and whether this association is mediated by changes in pain, mobility, and satisfaction**
3. **to explore the association between coping strategies/expectations before and after surgery, as measured by the SPOC questionnaire, and cognitive changes after surgery; and to explore the correlation between changes in SPOC and cognitive changes from preoperative to 4-6 weeks after surgery.**
4. **to qualitatively explore lived experiences of pain, mobility and aging, including resilience, expectations and satisfaction with surgery, in patients undergoing TKA or THA across different ages and comorbidities.**

The current protocol and ethics submission describes methods and seek ethics approval for specific objectives 1-3. Objective 4 will be covered in a separate protocol and ethics application.

3. METHODS

3.1 Study design and design modification

The ArthroCaP study includes a quantitative component, represented by a nested prospective cohort study (objectives 1-3), and a qualitative component, represented by a series of semi-structured interviews (objective 4). The current protocol describes the quantitative component.

The ArthroCaP study was initially designed as a sub-study of the ongoing "Determinants of Long-term Outcomes after Knee Arthroplasty: A Prospective Multicentre Cohort Study, also known as SPOC study. The SPOC study, approved by the Hamilton Integrated Research Ethics Board on March 11, 2019 (Project Number 5740), planned to enrol 388 ≥50 years old patients undergoing elective TKA in Hamilton (St Joseph's Hospital and Juravinski Hospital). Maintaining the same prospective cohort design of the main study, the ArthroCaP sub-study was designed to add 1) baseline and longitudinal cognitive/neuropsychological assessments, and 2) baseline and longitudinal blood collections for the measurement of specific biomarkers and the development of a biobank for the future evaluation of additional biomarkers as suggested by new evidence and hypotheses (overall referred to as "Biomarkers study", see 3.4.2).

After the initial approval of ArthroCaP, the recruitment in the main SPOC study has experienced a significant slow-down due to the cancellation or deferral of elective surgeries during the COVID pandemic. This has affected the ability to recruit also in the ArthroCaP sub-study and reduced the potential to reach the planned sample size before the termination of the SPOC study. Due to these circumstances, a decision was made by the ArthroCaP investigators to extend the recruitment in the ArthroCaP study beyond the termination of the SPOC study, and to include not only patients undergoing elective TKA (as in the SPOC study) but also those undergoing THA. The ArthroCaP study will maintain the same objectives and timeline. However, due to the extension beyond the termination of and population included in the SPOC study,

participants recruited not as part of the SPOC study will sign a new consent for participation in the ArthroCaP study, which includes those assessments that are necessary to answer the ArthroCaP research questions but that were initially performed as part of the SPOC study.

The following sections are described to reflect the most updated study methods."

3.2 Eligibility criteria

Patients are eligible to participate in ArthroCaP if they are:

1. aged 50 years or older,

2. scheduled for elective TKA for osteoarthritis and enrolled in the SPOC study*, or scheduled for THA for osteoarthritis

3. able to provide informed consent.

*After termination of the SPOC study, the enrolment in the SPOC study will no longer represent an inclusion criterion.

Patients will be excluded if any of the following *exclusion criteria* are met:

1. known history of dementia,
2. unavailability of tablet or computer with an internet connection for remote assessment,
3. patient unable to interact with a tablet or computer due to language, visual, or hearing impairment, or any severely limited mobility of the upper limb joints, OR
4. patient unable to understand spoken or written English.

3.3 Recruitment and procedures

While the SPOC study is still actively recruiting, the process of recruitment of eligible patients for the ArthroCaP study will coincide with that of the primary study, as described in the main SPOC protocol. Participants consenting to the "Determinants of Long-term Outcomes after Knee Arthroplasty: A Prospective Multicentre Cohort Study", and meeting the eligibility criteria for this sub-study, will be explained and asked to consent to the specific procedures for the sub-study. We will seek a specific patient consent to the additional baseline and longitudinal cognitive/neuropsychological assessments, and to the biomarker study, separately. In addition, for the biomarker study, a sub-study informed consent form will specifically and separately ask for consent to the storage of the blood sampling and to genetic analyses (see 3.4.2). Recruitment of patients after the termination of the SPOC study will follow similar procedures, however, the ArthroCaP study will be presented to the potential participants as one entity with all the assessments conducted by the sub-study team.

Eligible patients will be approached for the first time in person, between 1 month and 1 week before surgery, during the preoperative assessment visit or during a group exercise session ('knee class' or 'hip class'). Some of them are fully informed about the study and provide consent at the first approach; some of them opt to be emailed the informed consent form and are called to follow up on their decision to participate in the study. For patients who are emailed the consent form and explained the study during a phone call, an initially verbal consent will be sought in order to allow for the remote baseline preoperative assessments. A signed written consent form will be then obtained when the patients are admitted to the hospital. Once the

patient consents to the sub-study, the sub-study-specific assessments will be done in addition to and separately (i.e., on a separate virtual or in-person visit) from the main study assessments.

APPENDIX I summarizes the timeline, measurements, and data collection for the ArthroCaP study. The baseline and longitudinal assessments will occur in compliance with the local restrictions to research due to the COVID-19 pandemic and based on patient acceptance. Patient surveys will be completed over the phone or via videoconference. For cognitive/neuropsychological testing, the study will employ tools that are validated for remote administration, including online/electronic versions or versions adapted for administration through videoconference by trained personnel. For the baseline and every postoperative longitudinal assessment, patients will be invited to schedule a videoconference with the research personnel who will administer the tests or supervise the self-administration of the tests, depending on the specific test as described in 3.4.1. In case of change of the regulation currently in force, in-person assessments following the same timeline will be considered and offered to the participants as an option. Likewise, whenever the participant is due for clinical reasons for an in-person visit, which is occurring in agreement with the study timeline, the option of performing the study assessments during the in-clinic visit will be offered to the participant. If necessary, the participants will be allowed to involve in the study a next of kin or support person who can help facilitate the access to an electronic device with an internet connection which will be used for the study videoconferences and for the administration of the online web-based neuropsychological tests. The videoconference-based assessments will be conducted using any of the following software options which allow screen sharing, i.e., McMaster Zoom, Microsoft Teams or Webex, based on availability and participant discretion. We expect each study videoconference/visit for the cognitive/neuropsychological assessment to last between 45 and 60 minutes.

Blood drawing will occur based on the study timeline (**APPENDIX I**) and in agreement with research restrictions in force (see 3.4.2).

We will seek patient confirmation of consent to participate in the study at every in-person or virtual visit throughout the study.

3.4 Measurements

Patients who agree to participate in the ArthroCaP sub-study while the recruitment in SPOC is ongoing will undergo all the procedures and measurements outlined in the protocol for the main study. In particular, participants are assessed at baseline for their socio-demographics data, comorbidities, Physical Frailty Phenotype, health-related quality of life (EQ-5D), anxiety and depression (Hospital Anxiety and Depression Scale [HADS], pain, and pain medication. Pain scores (based on a numerical pain scale) and pain medications are assessed at baseline, and then 4-6 weeks, 3 months, 6 months and 12 months after surgery. The SPOC instrument is administered at baseline and repeated at 4-6 weeks after surgery. The presence and severity of CPSP and satisfaction (SAPS) are measured at 3, 6, and 12 months. Changes in health-related quality of life and clinical complications are also monitored and collected over time. For TKA and THA patients approached after the termination of the recruitment in SPOC, these measurements will be described in the ArthroCaP informed consent form and conducted by the ArthroCaP study team

using ArthroCaP-specific case report forms (CRFs), as done for the cognitive/neuropsychological assessment.

3.4.1 Cognitive/neuropsychological assessment

The baseline and cognitive/neuropsychological assessment will include the following (**APPENDIX I**):

1) The Montreal Cognitive Assessment (MoCA)

The MoCA (MoCA, https://www.mocatest.org)is a sensitive global cognitive screening tool, which evaluates multiple cognitive domains, including orientation, memory, language, attention, calculation, constructions/visuospatial skills, executive function, and abstraction.[26] Time to administer the MoCA is approximately 10-15 minutes. The total possible score is 30 points and is calculated as a sum of the sub-scores for each sub-task. The final score is adjusted for the influence of education, by adding one point for an individual who has 12 years or fewer of formal education. For the remote assessment we will use the validated Full MoCA version for administration through audio-visual conference (https://www.mocatest.org/remote-moca-testing/).

2) The Mnemonic Similarity Task (MST)

The classic MST consists of a series of 192 color photographs of everyday objects on a white background.[27] There are typically two phases: an incidental encoding phase, when participants engaged in an indoor/outdoor judgment for each picture (based on their opinion with no right or wrong answer); and a subsequent recognition test with a three-choice response. The objects include three stimulus types (each representing one third of the objects): exact repetitions of earlier items, lures that are similar but not identical to earlier items, and novel foils. During the test, participants are asked to identify each item as "Old," "Similar," or "New". The recognition memory score is calculated as the difference between the rate of "Old" responses given to repeat items minus "Old" responses given to foils. The lure discrimination index (which measures mnemonic discrimination) is calculated as the difference between the rate of "Similar" responses given to the lure items minus "Similar" responses given to the foils. Typically, 'normal' aging is associated with a decline in mnemonic discrimination (i.e. (identifying lure objects that are similar to memory set objects as "similar") with preserved recognition memory (identifying repeated memory set objects as "old").[28] The traditional MST as here described has been used also in older people.[29] [30] It is available in a format for online administration. We are working with the task developers (http://faculty.sites.uci.edu/starklab/mnemonic-similarity-task-mst/) to have a validated modified online version of MST ready for use by the launch of our study; the modified version is adapted to increase the efficiency of the test (i.e. to obtain the same information but with a shorter test) and therefore its acceptability with older participants.[29]

3) Additional neuropsychological testing

The following neuropsychological testing (available in electronic versions for online administration) will be additionally performed:

- the Visual Paired Associates Learning (PAL) test, designed after the Cambridge Neuropsychological Test Automated Battery (CANTAB) – PAL test, which measures hippocampal-dependent visuo-spatial memory by testing participant's memory for object location pairs. For this test (expected time requirement 10 minutes), boxes are

displayed on the screen and are opened in a randomized order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. If the participant makes an error, the patterns are re-presented to remind the participant of their locations. The difficulty level increases through the test;

- the Rapid serial Visual Presentation (RVP) test (designed after the CANTAB-RVP test), which assesses executive function (working memory and sustained attention). For this test (expected time requirement 7-10 minutes), a white box is shown in the centre of the screen, inside which digits from 2 to 9 appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8). When the participant sees the target sequence they must respond by selecting the button in the centre of the screen as quickly as possible. The level of difficulty varies with either one- or three-target sequences that the participant must watch for at the same time.
- the N-back test, which assesses visual working memory. For this task (expected time requirement 7-10 minutes), participants are shown a series of numbers on the screen, and are occasionally asked to enter the number they saw 2 numbers ago; AND
- the Stroop word colour interference task, which assesses inhibitory control. For this test (expected time requirement 5-10 minutes), participants will be tested on their ability to identify the color of the word, not what the word actually states. This acts as a test of attention by tapping the ability to suppress a habitual response in favor of a less familiar one, and provides additional indices of simple attention like word reading and color identification.

4) Subjective Memory Complaints (SMC)

We will also assess Subjective Memory Complaints (SMC).[31] Participants will be asked the following 4 questions: i) “Do you have any difficulty with your memory?” ii) “Do you forget where you have left things more than you used to?” iii) “Do you forget the names of close friends or relatives?” and iv) “Do other people find you forgetful?”. A positive response to any of these questions will indicate SMC.[32 33]

3.4.2 Biomarkers study

Participants who consent to the biomarker study will have their blood drawn when they are admitted to the hospital on the morning of surgery, before surgery. For the postoperative time points we will take into account the current changes in the modality of hospital admission for elective TKA due to the pandemic. A larger number of elective TKA are currently booked as same day procedures, with the patients being discharged on the same day of surgery. Therefore, every study participant, regardless of the type of hospital admission and actual length of stay, will have their blood for the biomarker study drawn 2-4 hours after surgery. Participants who stay at least one night in the hospital after surgery will also have their blood drawn daily from postoperative 1 to postoperative day 3, or to the day of discharge (whichever comes first), with the blood being preferentially drawn in the morning and with fasting. Tentatively, blood will be also collected at 4-6 weeks after surgery when patients who underwent TKA typically have their surgical follow-up. Currently, during the pandemic, ≥50% of participants are having an in-clinic visit. We expect that for ≥80% of the participants we will be able to have blood samples at 12

months after surgery. The opportunity to collect blood at 6 months in at least a subset of participants will depend on the evolution of the pandemic and the ability to have in-person research visits. **APPENDIX I** summarizes the timeline for blood collection.

For the biomarkers study, patients will be asked consent separately for each of the three following research activities: 1) consent to have their blood drawn for measurement on plasma of specific biomarkers, i.e. neurotrophic factors and N-terminal pro–B-type natriuretic peptide (NT-proBNP); 2) consent to have their blood drawn and stored for future tests (biobank); and 3) consent to have their blood drawn (and stored) for current and future testing on genetic material.

We will measure longitudinally the levels of neurotrophic factors that have showed promising results as possible mediators of the effect of physical performance (and, we hypothesize, pain and satisfaction), on neuroplasticity (and possibly cognitive performance), i.e. the *brain-derived neurotrophic factor* (BDNF) and the *insulin-like growth factor-1* (IGF-1).[23] We will include the measurement of the *nerve growth factor* (NGF), another neurotrophic factor that has been associated with neuron survival and cognitive performance.[34] We will also measure NT-proBNP. Preoperative NT-proBNP levels have been demonstrated to be a strong independent predictor of major postoperative outcomes after non-cardiac surgery.[35] However, the role of NT-proBNP in predicting postoperative cognitive outcomes has been not assessed. Moreover, NT-proBNP is usually measured preoperatively whereas the dynamic changes of its perioperative and postoperative levels, and their correlation with postoperative outcomes, have never been evaluated. Interestingly, NT-proBNP has been shown to correlate with measures of physical performance and tolerance (like peak oxygen consumption, VO_2 peak) which could be affected by persistent pain and could affect satisfaction. We will explore how the changes on NT-proBNP also correlate with changes in pain and satisfaction, as well as with changes in neurotrophic factors levels.

We will measure the plasma levels of neurotrophic factors but also their RNA expression in blood leukocytes. For participants who agree to have their blood samples stored in the biobank and also to have their genetic material tested, we will explore other mechanistic hypotheses and other possible biomarkers in the field of CPSP and POCD from plasma but also RNA expression and DNA.

At each time point, we will collect venous blood into EDTA tubes (from which to obtain both plasma and whole blood for DNA measurements) and RNA PAXGene tubes for blood RNA analysis. At each time point, we will collect overall (i.e. for specific biomarkers measurements and for the biobank) 10 ml of blood in EDTA and 10 ml of blood in RNA PAXGene tubes. If a patient does not consent to genetic testing, no RNA PAXGene tube will be collected and the EDTA blood will be used only for analyses on plasma and not for DNA testing. If a patient does not consent to biobanking but does consent to genetic testing, we will collect only half of the amount of blood into the 2 different types of tubes. Samples will be collected at the participating hospitals into pre-prepared study kits, and processed and aliquoted on site based on standard procedures as defined in a specific study manual. In particular, blood samples will be incubated in the RNA PAXgene tubes for a minimum of 2 hours at room temperature to completely lyse blood cells; they will be then frozen first at -20ºC for 24 hours, then transferred to -80ºC, upright in a wire rack. Samples will be batched, and transported to the Clinical Research Laboratory and Biobank (CRLB) - Genetic and Molecular Epidemiology Laboratory (GMEL) at the Hamilton Health Sciences, General Hospital Site. Part of the samples will be remain at the CRLB-GMEL and used

for NT-proBNP testing and for biobanking. From the CRLB-GMEL, part of the aliquots will be transported to Prof. Fahnestock's laboratory at the McMaster University Health Sciences Centre for neurotrophic biomarkers measurement.

3.5 Sample size

The ArthroCaP study has been designed as a proof-of-concept study, hypothesis-generating, with exploratory objectives. Based on the original recruitment rate in the main SPOC study, we expected to be able recruit in the sub-study $\geq$150 of the planned 388 SPOC participants. Although exploratory, enrolling ≥150 participants would give us a power of ≥80% to detect an association between moderate-severe CPSP at 6 months and ≥2 point decline in MoCA at 1 year, with an Odds Ratio of 2.5-3.0 when we consider some residual correlation between independent variables (i.e., $R^2 \leq 0.3$ even after removing collinear covariates. This was based on the assumptions that 20% of the study participants will experience ≥2 point decline in MoCA at 1 year (considering the possibly younger age and different surgery representation in our study compared to NeuroVISION-1), and that 30% will present moderate-severe CPSP at 6 months (see sample size calculation for the main SPOC study).

Due to the disruptions to recruitment secondary to the pandemic, we modified our target sample size to 100 patients, aware that the study will provide preliminary nondefinitive data to inform future research. This is consistent with the intent of the catalyst grant that supports the study.

3.6 Statistical analyses

Baseline characteristics will be summarized through descriptive statistics, i.e. mean (standard deviation), median (interquartile range [IQR]), or number (%) as appropriate.

Objective 1. We will first evaluate the primary study objective modeling longitudinal changes in pain scores (independent variable) and changes in cognitive/neuropsychological scores (dependent variable) over time (4 weeks, and 3, 6, and 12 months after surgery) using multilevel (mixed effects) regression models, considering time points nested within patients.[36] Secondarily, in mixed effects models, we will specifically look at whether experiencing moderate-severe persistent pain at 3 months after surgery (or at 6 months after surgery) predicts subsequent decline in cognitive performance (i.e. at 6 and 12 months, or at 12 months).[9] Models will be adjusted for relevant covariates, including baseline characteristics (at the patient level, e.g. age, sex, comorbidity index, and anxiety/depression level) and pain medications as time-varying variables. We will adopt a parsimonious approach in covariates selection, based on clinical relevance and removing collinear covariates (i.e., variance inflation factor >2.5) according to pre-specified priorities. We will use the same statistical approach to look at the association between satisfaction (measured with the SAPS instrument) and cognitive performance.

Objectives 2. We will explore our objective 2a, analyzing separately change in MST scores and changes in other cognitive performance measures. Bonferroni correction of alpha values will be adopted to adjust for multiple comparisons. For the biomarker study (objective 2b), we will similarly model mixed effects regression models to evaluate how the biomarker levels change over time and how these changes correlate with changes in pain, satisfaction, and cognitive performance. We will also analyze whether biomarkers levels at baseline (before surgery), and

right after surgery (or at 4-6 weeks after surgery) predict cognitive changes/decline at 6 and 12 months.

Objective 3. To evaluate the role of coping abilities and expectations, as measured by the SPOC questionnaire, we will first analyze the association between baseline SPOC and baseline cognitive performance in a traditional multivariable linear regression analysis; similarly, we will analyze the association between early postoperative (4-6 weeks) SPOC and cognitive performance, after adjusting for baseline measurements. Then we will analyze whether preoperative and postoperative SPOC predict cognitive decline at 6 and 12 months using linear and logistic (i.e. with ≥2 point decline in MoCA as binary outcome) regression models.

All the analyses for all the objectives will be first conducted in the overall sample of study participants. As additional analysis, we will explore whether there is a signal for any subgroup effect based on the type of surgery performed, i.e., knee versus hip arthroplasty. We will undertake such exploratory subgroup analyses as long as both subpopulations reach at least 30% of representation.

4. IMPORTANCE OF THE STUDY

"My father hasn't been quite the same since his surgery…" As doctors, and as children, many of us have had and reported such experience. Anesthetic-related mortality has decreased 100-fold over the last 100 years. However, when asked about their fears related to undergoing major surgery with general anesthesia, people, across different ages, indicate 'brain damage' and 'memory loss' as main concerns, much more frequently than perioperative death.[37] Moreover, the literature shows that, even with only a partial understanding of the concept of likelihood, most older people would not choose a treatment when the expected outcome is survival, if associated with cognitive and functional impairment.[38 39] CPSP is highly prevalent in older people undergoing surgery, and in particular major orthopedic surgery; in the older surgical populations, also persistent postoperative cognitive dysfunction is highly prevalent. Both these conditions are associated with reduced autonomy and increased burden to patients, caregivers, and healthcare systems.

On the other side, the existing literature shows a decrease in quality of life in people with chronic pain waiting for >6 months for assessment;[40] and that people waiting for their major joint surgery tend to report that their waiting time is contributing significantly to the deterioration of their health.[41] Likewise, the current experience with COVID and the deferral of elective surgeries is bringing to our attention what holding such treatment might mean to older people with chronic conditions. Our study will provide preliminary data on the role of chronic pain, and chronic pain medications, in the impact of surgery on older people's cognitive abilities, and on the underlying mechanisms. It will inform larger confirmatory studies, and finally the design of interventions to enhance the benefits of surgery.

APPENDIX I. Study timeline, measurements, and data collection

	Before surgery			After surgery			
Measurement	**Day -28 to -1**	**Day of surgery**	**Day of surgery (2-4 hours after surgery)**	**+4-6 weeks**	**+3 mo**	**+6 mo**	**+12 mo**
	Online - Videoconference with research team or in person	**In person**	**In person**	**Online - Videoconference with research team or In person**			
Socio-demographics	x						
Comorbidities/ Medical History	X						
Surgical characteristics				x			
Pain Medication Usage	x			x	x	x	x
The Somatic Preoccupation and Coping (SPOC) Questionnaire	x			x			
FRAIL Scale (Frailty assessment)	X						
Hospital Anxiety and Depression Scale (HADS)	X						
Pain Assessment	x			x	x	x	x
Self-Administered Patient Satisfaction (SAPS) Scale					x	x	x
Complications				x	x	x	x
Cognitive/ neuropsychological assessment - MoCA - MST	x			x		x	x

- Other neuropsychological testing - SMC							
Blood drawing for biomarker study		x	x*	x**		x**	x**

*the subset of patients that stay in hospital at least one night after surgery will have blood collected also every morning on postoperative day 1-3, or until discharge (whichever comes first)

**whenever an in person study visit is feasible depending on restrictions in place due to the pandemic and patient compliance

MoCA, Montreal Cognitive Assessment; MST, Mnemonic Similarity Task; SMC, Subjective Memory Complaints

REFERENCES

1. Evered LA, Silbert BS. Postoperative Cognitive Dysfunction and Noncardiac Surgery. *Anesth Analg* 2018;127(2):496-505. doi: 10.1213/ANE.0000000000003514
2. Evered L, Silbert B, Knopman DS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Can J Anaesth* 2018;65(11):1248-57. doi: 10.1007/s12630-018-1216-x
3. Newman S, Stygall J, Hirani S, et al. Postoperative cognitive dysfunction after noncardiac surgery: a systematic review. *Anesthesiology* 2007;106(3):572-90. doi: 00000542-200703000-00023 [pii] [published Online First: 2007/02/28]
4. Neuro VI. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. *Lancet* 2019;394(10203):1022-29. doi: 10.1016/S0140-6736(19)31795-7
5. Krishnan K, Rossetti H, Hynan LS, et al. Changes in Montreal Cognitive Assessment Scores Over Time. *Assessment* 2017;24(6):772-77. doi: 10.1177/1073191116654217
6. Tan HH, Xu J, Teoh HL, et al. Decline in changing Montreal Cognitive Assessment (MoCA) scores is associated with post-stroke cognitive decline determined by a formal neuropsychological evaluation. *PLoS One* 2017;12(3):e0173291. doi: 10.1371/journal.pone.0173291
7. Berger M, Nadler JW, Browndyke J, et al. Postoperative Cognitive Dysfunction: Minding the Gaps in Our Knowledge of a Common Postoperative Complication in the Elderly. *Anesthesiol Clin* 2015;33(3):517-50. doi: 10.1016/j.anclin.2015.05.008
8. Mazza S, Frot M, Rey AE. A comprehensive literature review of chronic pain and memory. *Prog Neuropsychopharmacol Biol Psychiatry* 2018;87(Pt B):183-92. doi: 10.1016/j.pnpbp.2017.08.006 [published Online First: 2017/08/12]
9. Whitlock EL, Diaz-Ramirez LG, Glymour MM, et al. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. *JAMA Intern Med* 2017;177(8):1146-53. doi: 10.1001/jamainternmed.2017.1622 [published Online First: 2017/06/07]
10. Rice DA, Kluger MT, McNair PJ, et al. Persistent postoperative pain after total knee arthroplasty: a prospective cohort study of potential risk factors. *Br J Anaesth* 2018;121(4):804-12. doi: 10.1016/j.bja.2018.05.070 [published Online First: 2018/09/22]
11. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg* 2006;102(4):1255-66. doi: 10.1213/01.ane.0000198602.29716.53 [published Online First: 2006/03/23]
12. Laigaard J, Bache N, Stottmeier S, et al. Cognitive Function During Opioid Tapering in Patients with Chronic Pain: A Prospective Cohort Study. *J Pain Res* 2020;13:3385-94. doi: 10.2147/JPR.S273025 [published Online First: 2020/12/29]
13. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane

Reviews. *Cochrane Database Syst Rev* 2017;10:CD012509. doi: 10.1002/14651858.CD012509.pub2 [published Online First: 2017/10/31]
14. Wu YH, Liu LK, Chen WT, et al. Cognitive Function in Individuals With Physical Frailty but Without Dementia or Cognitive Complaints: Results From the I-Lan Longitudinal Aging Study. *J Am Med Dir Assoc* 2015;16(10):899 e9-16. doi: 10.1016/j.jamda.2015.07.013 [published Online First: 2015/09/01]
15. Mahomed N, Gandhi R, Daltroy L, et al. The self-administered patient satisfaction scale for primary hip and knee arthroplasty. *Arthritis* 2011;2011:591253. doi: 10.1155/2011/591253 [published Online First: 2011/11/03]
16. Becker S, Wojtowicz JM. A model of hippocampal neurogenesis in memory and mood disorders. *Trends Cogn Sci* 2007;11(2):70-6. doi: 10.1016/j.tics.2006.10.013 [published Online First: 2006/12/19]
17. Han X, Wu Y, Zhong Y, et al. Recovery of High Interference Memory in Spite of Lingering Cognitive Deficits in a Longitudinal Pilot Study of Hospitalized Depressed Patients. *Front Psychiatry* 2020;11:736. doi: 10.3389/fpsyt.2020.00736 [published Online First: 2020/08/28]
18. Snyder JS, Soumier A, Brewer M, et al. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature* 2011;476(7361):458-61. doi: 10.1038/nature10287 [published Online First: 2011/08/05]
19. Gandy K, Kim S, Sharp C, et al. Pattern Separation: A Potential Marker of Impaired Hippocampal Adult Neurogenesis in Major Depressive Disorder. *Front Neurosci* 2017;11:571. doi: 10.3389/fnins.2017.00571 [published Online First: 2017/11/11]
20. Stark SM, Kirwan CB, Stark CEL. Mnemonic Similarity Task: A Tool for Assessing Hippocampal Integrity. *Trends Cogn Sci* 2019;23(11):938-51. doi: 10.1016/j.tics.2019.08.003 [published Online First: 2019/10/11]
21. Camfield DA, Fontana R, Wesnes KA, et al. Effects of aging and depression on mnemonic discrimination ability. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 2018;25(3):464-83. doi: 10.1080/13825585.2017.1325827 [published Online First: 2017/05/17]
22. Dery N, Pilgrim M, Gibala M, et al. Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. *Front Neurosci* 2013;7:66. doi: 10.3389/fnins.2013.00066 [published Online First: 2013/05/04]
23. Heisz JJ, Clark IB, Bonin K, et al. The Effects of Physical Exercise and Cognitive Training on Memory and Neurotrophic Factors. *J Cogn Neurosci* 2017;29(11):1895-907. doi: 10.1162/jocn_a_01164 [published Online First: 2017/07/13]
24. Busse JW, Bhandari M, Guyatt GH, et al. Development and validation of an instrument to predict functional recovery in tibial fracture patients: the Somatic Pre-Occupation and Coping (SPOC) questionnaire. *J Orthop Trauma* 2012;26(6):370-8. doi: 10.1097/BOT.0b013e31822421e2 [published Online First: 2011/10/21]
25. Khan JS, Devereaux PJ, LeManach Y, et al. Patient coping and expectations about recovery predict the development of chronic post-surgical pain after

traumatic tibial fracture repair. *Br J Anaesth* 2016;117(3):365-70. doi: 10.1093/bja/aew225 [published Online First: 2016/08/21]
26. Nasreddine ZS, Phillips NA, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x
27. Yassa MA, Stark CE. Pattern separation in the hippocampus. *Trends Neurosci* 2011;34(10):515-25. doi: 10.1016/j.tins.2011.06.006 [published Online First: 2011/07/27]
28. Stark SM, Yassa MA, Lacy JW, et al. A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia* 2013;51(12):2442-9. doi: 10.1016/j.neuropsychologia.2012.12.014 [published Online First: 2013/01/15]
29. Stark SM, Stevenson R, Wu C, et al. Stability of age-related deficits in the mnemonic similarity task across task variations. *Behav Neurosci* 2015;129(3):257-68. doi: 10.1037/bne0000055 [published Online First: 2015/06/02]
30. Bennett IJ, Stark SM, Stark CEL. Recognition Memory Dysfunction Relates to Hippocampal Subfield Volume: A Study of Cognitively Normal and Mildly Impaired Older Adults. *J Gerontol B Psychol Sci Soc Sci* 2019;74(7):1132-41. doi: 10.1093/geronb/gbx181 [published Online First: 2018/02/06]
31. Mitchell AJ, Beaumont H, Ferguson D, et al. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand* 2014;130(6):439-51. doi: 10.1111/acps.12336 [published Online First: 2014/09/16]
32. Tsutsumimoto K, Makizako H, Doi T, et al. Subjective Memory Complaints are Associated with Incident Dementia in Cognitively Intact Older People, but Not in Those with Cognitive Impairment: A 24-Month Prospective Cohort Study. *Am J Geriatr Psychiatry* 2017;25(6):607-16. doi: 10.1016/j.jagp.2016.12.008 [published Online First: 2017/02/22]
33. Schmand B, Jonker C, Hooijer C, et al. Subjective memory complaints may announce dementia. *Neurology* 1996;46(1):121-5. doi: 10.1212/wnl.46.1.121 [published Online First: 1996/01/01]
34. Fahnestock M, Shekari A. ProNGF and Neurodegeneration in Alzheimer's Disease. *Front Neurosci* 2019;13:129. doi: 10.3389/fnins.2019.00129 [published Online First: 2019/03/12]
35. Duceppe E, Parlow J, MacDonald P, et al. Canadian Cardiovascular Society Guidelines on Perioperative Cardiac Risk Assessment and Management for Patients Who Undergo Noncardiac Surgery. *Can J Cardiol* 2017;33(1):17-32. doi: 10.1016/j.cjca.2016.09.008 [published Online First: 2016/11/21]
36. Austin PC, Goel V, van Walraven C. An introduction to multilevel regression models. *Can J Public Health* 2001;92(2):150-4. [published Online First: 2001/05/08]
37. Matthey P, Finucane BT, Finegan BA. The attitude of the general public towards preoperative assessment and risks associated with general anesthesia. *Can J Anaesth* 2001;48(4):333-9. doi: 10.1007/BF03014959

38. Fried TR, McGraw S, Agostini JV, et al. Views of older persons with multiple morbidities on competing outcomes and clinical decision-making. *J Am Geriatr Soc* 2008;56(10):1839-44. doi: 10.1111/j.1532-5415.2008.01923.x
39. Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002;346(14):1061-6. doi: 10.1056/NEJMsa012528
40. Lynch ME, Campbell F, Clark AJ, et al. A systematic review of the effect of waiting for treatment for chronic pain. *Pain* 2008;136(1-2):97-116. doi: 10.1016/j.pain.2007.06.018 [published Online First: 2007/08/21]
41. Snider MG, MacDonald SJ, Pototschnik R. Waiting times and patient perspectives for total hip and knee arthroplasty in rural and urban Ontario. *Can J Surg* 2005;48(5):355-60. [published Online First: 2005/10/27]