

BMJ Open Examination of psychological risk factors for chronic pain following cardiac surgery: protocol for a prospective observational study

Michael H McGillion,^{1,2} Shaunattonie Henry,^{1,2} Jason W Busse,^{3,4} Carley Ouellette,^{1,2} Joel Katz,⁵ Manon Choinière,⁶ Andre Lamy,^{2,4} Richard Whitlock,^{2,4} Shirley Pettit,² Jacqueline Hare,² Krysten Gregus,² Katheryn Brady,² Nazari Dvirnik,^{2,4} Stephen Su Yang,^{2,4} Joel Parlow,⁷ Deborah Dumerton-Shore,⁸ Ian Gilon,⁷ D Norman Buckley,³ Harsha Shanthanna,³ Sandra L Carroll,¹ Peter C Coyte,⁹ Shanil Ebrahim,⁴ Wannudee Isaranuwachai,⁹ Denise N Guerriere,⁹ Jeffrey Hoch,¹⁰ James Khan,³ Joy MacDermid,¹¹ Geraldine Martorella,¹² J Charles Victor,⁹ Judy Watt-Watson,¹³ Kimberly Howard-Quijano,¹⁴ Aman Mahajan,¹⁴ Matthew T V Chan,¹⁵ Hance Clarke,¹⁶ P J Devereaux^{2,4}

To cite: McGillion MH, Henry S, Busse JW, *et al*. Examination of psychological risk factors for chronic pain following cardiac surgery: protocol for a prospective observational study. *BMJ Open* 2019;**9**:e022995. doi:10.1136/bmjopen-2018-022995

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2018-022995>).

Received 5 July 2018

Revised 15 November 2018

Accepted 16 November 2018



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Michael H McGillion;
mmcgill@mcmaster.ca

ABSTRACT

Introduction Approximately 400 000 Americans and 36 000 Canadians undergo cardiac surgery annually, and up to 56% will develop chronic postsurgical pain (CPSP). The primary aim of this study is to explore the association of pain-related beliefs and gender-based pain expectations on the development of CPSP. Secondary goals are to: (A) explore risk factors for poor functional status and patient-level cost of illness from a societal perspective up to 12 months following cardiac surgery; and (B) determine the impact of CPSP on quality-adjusted life years (QALYs) borne by cardiac surgery, in addition to the incremental cost for one additional QALY gained, among those who develop CPSP compared with those who do not.

Methods and analyses In this prospective cohort study, 1250 adults undergoing cardiac surgery, including coronary artery bypass grafting and open-heart procedures, will be recruited over a 3-year period. Putative risk factors for CPSP will be captured prior to surgery, at postoperative day 3 (in hospital) and day 30 (at home). Outcome data will be collected via telephone interview at 6-month and 12-month follow-up. We will employ generalised estimating equations to model the primary (CPSP) and secondary outcomes (function and cost) while adjusting for prespecified model covariates. QALYs will be estimated by converting data from the Short Form-12 (version 2) to a utility score.

Ethics and dissemination This protocol has been approved by the responsible bodies at each of the hospital sites, and study enrolment began May 2015. We will disseminate our results through CardiacPain.Net, a web-based knowledge dissemination platform, presentation at international conferences and publications in scientific journals.

Trial registration number NCT01842568.

Strengths and limitations of this study

- This is a prospective, multisite study with a large cohort of cardiac surgery patients.
- One-year follow-up is compliant with Initiative for Methods, Measurement, and Pain Assessment in Clinical Trials recommendations to standardise timing of outcome assessment for prognostic studies of chronic postsurgical pain (CPSP).
- A robust analysis plan using generalised estimating equations will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6 months and 1 year while adjusting for prespecified covariates.
- Assiduous follow-up procedures will be adhered to, which have been proven effective in prior prospective observational studies.
- There is reliance on pain and quality of life self-report outcome measures; however, rigorous criteria to define CPSP will be applied, and valid and reliable instruments will be used.

INTRODUCTION

Approximately 400 000 Americans and 36 000 Canadians undergo cardiac surgery annually, and these numbers are expected to rise as the population ages.^{1–5} Despite the proven survival and symptom-related benefits of cardiac surgeries, mounting evidence suggests that chronic postsurgical pain (CPSP)—and related poor functional recovery—following these procedures are major clinical problems.^{6–31} Moreover, the

economic consequences of persistent pain and dysfunction remain uncertain. Identification of factors associated with the development of CPSP could facilitate efforts to improve outcomes among high-risk patients, yet the majority of putative risk factors examined to date are not tenably modifiable in the perioperative context. Three psychological factors that do show promise as modifiable, potential risk factors for CPSP include pain-related beliefs, gender-based pain expectations and somatic preoccupation and coping. The purpose of this study is to examine whether these factors are associated with transition to CPSP following cardiac surgery.

CPSP following cardiac surgery

Due to conceptual and methodological differences in the assessment of pain, and conflicting opinions about the duration of ‘chronicity’, there is no one accepted definition of CPSP.³² However, there is consensus among experts^{32–38} that CPSP should meet the minimum criteria, set forth by Macrae and Davies³³ and others,^{34–40} as follows. It must: (A) have developed after the surgical procedure, (B) be different from pain experienced prior to the procedure, (C) not be caused by other factors (eg, cancer recurrence and chronic infection), (D) be present for at least 2–3 months and (E) interfere significantly with health-related quality of life.^{34–40}

Open cardiac surgeries involve many pain-sensitive structures, as they require a median sternotomy, retraction of the ribs and invasion of muscles and visceral tissues. In coronary artery bypass surgery (CABG), the grafting procedure requires harvesting at several sites including, most commonly, the internal mammary artery (IMA). The manipulation and retraction of the sternum as well as the use of electrocautery to dissect the IMA from the chest wall may result in nerve damage that leads to intercostal neuralgia.^{41–44} The greater and lesser saphenous veins are also used as grafts in CABG surgery and require significant leg incisions. These procedures may result in pain that can last for variable periods and may be inflammatory or neuropathic in nature. CPSP in cardiac surgery patients is often experienced in the thorax and legs but has also been described, to a lesser degree, in the shoulders, back and neck.^{10 12 45} The pathophysiological pathways underlying CPSP are multifactorial. Tissue damage leads to release of high concentrations of bradykinin, adenosine, lactate and potassium in the peripheral microenvironment, thereby causing nociceptor activation.^{46 47} These mediators activate capsaicin-sensitive TRVP1 receptors, which serve as the primary transducer of the noxious stimulus.⁴⁷ Other neurochemicals, such as the neuropeptides substance P and calcitonin gene-related peptide, further augment pain.⁴⁷ These peripheral nociceptive processes are modulated in the central nervous system by mechanisms involving selection, abstraction and synthesis of information from the total sensory input.⁴⁸ The amount, quality and nature of the pain experienced are therefore dynamic and multidimensional products of sensory-discriminative,

cognitive-evaluative and affective-motivational components.⁴⁸ Like any form of chronic pain, ongoing pain after surgery can lead to pathological nervous system changes, collectively known as sensitisation⁴⁷—a function of what we now understand to be neuronal modifiability.⁴⁶ Sensitisation of the nervous system may lead to increased pain sensitivity (hyperalgesia), augmentation of the normal duration (hyperpathia) amplitude of pain, perception of non-painful stimuli as painful (allodynia)^{47 49} and abnormal, unpleasant hypersensitivity (dysesthesia).⁵⁰

As Katz and Seltzer argued,³² critical to understanding the nature of CPSP is appreciating that in each case, the pain was once acute and involved a transition phase. There is much work to be done to continue to develop our understanding of risk factors, which predispose cardiac surgical patients to pain chronicity.

Prevalence and consequences

We reviewed 26 published/under review studies to date, across 14 countries,^{6–31} which have examined the prevalence and/or factors associated with CPSP following cardiac surgery. On careful examination of the available data, it is important to recognise that cross-sectional and retrospective studies have generally reported higher prevalence rates (14%–56%) than those investigations with prospective designs (7.5%–45%). In the recent (2013) large-scale Canadian CARDpain study (n=1010), Choinière *et al*²⁸ reported CPSP prevalence rates of 40%, 22% and 17% at 3, 6, and 12 months following cardiac surgery, respectively. Routledge *et al*³¹ found similar prevalence rates of CPSP in their prospective extension (Women’s Recovery from Sternotomy-Extension (WREST-E)) of a randomised clinical trial (Women’s Recovery from Sternotomy (WREST)) (n=222) to examine the impact of a novel compression undergarment on women’s recovery from median sternotomy (3 months postoperative [post-op]: 41%; 12 months post-op: 16.7%). In contrast to CARDpain and WREST-E, 1 year CPSP prevalence rates as high as 39% and 45% have been reported in prospective studies of patients following CABG in Turkey²⁷ and the Netherlands.³⁰ Aside from differences in study design, the observed variability in reported prevalence rates of CPSP after cardiac surgery may be explained by the use of point prevalence versus cumulative prevalence, variability with respect to the operational definitions of CPSP, timing of outcome measurement and duration of follow-up period.

CPSP has been associated with the development of anxiety and depressive disorders,^{51–55} sleep disturbances and fatigue,^{56–60} as well as poor self-rated health.^{7 51 53 61} For example, among those with CPSP in the CARDpain study, over 50% reported significant pain-related interference with activities of daily living—including family and home responsibilities, recreation and employment—at 3, 6 and 12 months following cardiac surgery.^{28 62}

Risk factors for CPSP

Several studies have attempted to establish risk factors for CPSP in cardiac surgery patients.

Their limitations can be summarised⁶³ as: (1) many studies focused on univariate analyses, or were insufficiently powered to employ multivariate modelling techniques, (2) the vast majority of risk factors examined to date are not tenably modifiable in the perioperative context, (3) psychological risk factors (affective and cognitive) are substantially understudied in comparison with demographic, clinical/surgical and analgesic risk factors, constituting a major gap and (4) although retrospective and cross-sectional studies provide some insight on potential variables associated with CPSP, cross-sectional studies lack the temporal orientation to make solid inferences about putative, causal relationships and retrospective studies can be limited by availability and quality of data. In addition, even robust retrospective may be limited in terms of risk factors explored and related data collection methods. Risk factors for CPSP can be classified into four categories: (A) demographic, (B) baseline clinical, technical-surgical, and hospitalisation-related factors, (C) acute post-op pain and (D) psychological factors.

Demographic factors

Demographic factors examined include age, sex, level of education, body mass index (BMI) and smoking history. Younger age has been positively associated with CPSP^{7 9 12 17 20 25 28} in multiple retrospective, cross-sectional and prospective studies, as observational data embedded within randomised controlled trials (RCTs); significant ORs have ranged from 1.43 to 7.03 in cases where this outcome was dichotomised (ie, younger vs older patients). However, four of the more recent published studies to date (one retrospective,¹⁷ one cross-sectional,¹⁸ one RCT⁵⁰ and one prospective²¹) have found no positive association between age and the development of CPSP. Conflicting findings have also been reported for sex. Although some studies indicate higher risk of CPSP with women,^{21 29 30} multiple studies with divergent designs^{9 12 14 18 20 28 48} have reported no significant association between sex and the development of CPSP. Examination of BMI as a risk factor for CPSP has also produced mixed results. While two studies (one cross-sectional⁷ and one RCT [embedded observational data],²⁰ ORs=1.34 and 9.05, respectively) provided supportive evidence, other cross-sectional^{17 18} and prospective studies^{9 28} found no association between CPSP and BMI (OR range: 1.02–1.1). Finally, we are aware of two prospective studies to date that have examined the association of CPSP with formal level of education²⁸ and smoking history,¹⁴ respectively; no significant association was found in either case.

Baseline clinical, surgical and hospitalisation-related factors

Among baseline clinical factors, neither a history of diabetes mellitus^{9 14 17 23 24 50} or peripheral arterial disease²⁴ have been significantly associated with the development of CPSP.

However, pre-existing peripheral arterial disease has been examined as a risk factor in just one retrospective

study²⁴ to date. Similar to diabetes mellitus, the majority of prospective studies^{20 21 23} (including one RCT)²⁰ reported no predictive ability of baseline chronic pain conditions in the literature (OR=1.00–1.04, where reported). To date, CARDpain²⁸ is the only prospective examination to report that pre-existing chronic pain at baseline (non-anginal) is positively associated with CPSP (adjusted OR=1.44, 95% CI 1.12 to 1.86).²⁸

The evidence pertaining to the predictive value of preoperative angina is also mixed. Two cross-sectional studies reported preoperative angina that was positively associated with CPSP (OR, where reported=1.62)^{7 12}; however, another cross-sectional¹⁷ and two additional large-scale prospective studies^{14 28} found no significant associations to infer that preoperative angina is a significant risk factor for CPSP.

The majority of studies have reported no association^{6 12 13 17 22 28 50} between a range of surgical factors, including: (A) type of surgical technique, (B) number and type of bypass grafts per operation, (C) harvesting technique and (D) total cross-clamp time (ie, total time aorta is clamped to separate systemic circulation from cardiac outflow) and the development of CPSP. There is some evidence to suggest that not skeletonising the internal thoracic artery harvest (ie, harvesting it along with its surrounding pedicle of vascular tissue) is more likely to invoke CPSP⁶⁴; those who have undergone left IMA harvesting may also be at higher risk.^{13 42} In general, post-op complications and related adverse events (eg, reoperation for bleeding and infections) have not been associated with CPSP,^{9 12 14 16 20 28} with the exception of one prospective study that identified post-op re sternotomy as a significant risk factor (OR=3.38).²¹ Cardiac surgeries of longer duration (ie, total OR time)^{18 20} also do not seem predictive of CPSP; in fact, the CARDpain²⁸ study found that the longer the OR time, the less likely CPSP was to develop. Finally, there seems to be no conclusive evidence to suggest that length of time in the intensive care unit,^{18 20 28} or total duration of hospitalisation¹⁸ contribute to the development of CPSP after cardiac surgery.

Acute post-op pain

Two prospective studies found that severe pain (ie, numeric rating scale [NRS] $\geq 7/10$) on post-op day 3 was a significant risk factor for CPSP at 1-year follow-up,²¹ as well as worst and average pain ratings at 2-year follow-up.²⁸ A third prospective study found that severe pain on post-op day 30 positively predicted CPSP at 3 months.²³ The association between analgesic therapy and CPSP is uncertain.^{10–12 18 19 21 23 27 28}

Psychological factors

Only the CARDpain²⁸ study has examined the role of psychological risk factors in the development of CPSP and found that presurgical anxiety, as measured by the Hospital Anxiety and Depression Scale (HADS), was a significant risk factor, with a 10% increase in the odds of

developing CPSP for each unit increase in HADS-A scale scores (OR=1.10, 95% CI 1.06 to 1.14). Other psychological risk factors examined (catastrophising and depression) demonstrated no association.

Genetic factors

Several members of this investigative team (eg, HC and JK) are involved in studies investigating the influence of genetic polymorphisms on the development of CPSP after cardiac and other types of surgery. The science of pain genetics is evolving; investigations of this nature are complex, requiring extensive research infrastructure for genotyping and related proteomic methods. Controlling for the influence of genetic factors is beyond the scope of this study.

Conceptual underpinnings and study focus

To address the above noted gap in the research to date, our primary objective is to examine the potential influence of psychological factors on the development of CPSP after cardiac surgery. Clear justification for the specific putative risk factors to be measured requires that we first explicate the conceptual underpinnings of our study. Given the complexity of the multidimensional pain experience, there are many ways to conceptualise CPSP.⁶⁵ We are aligned with the biobehavioural view of pain, espoused by international leaders in the science of the cognitive and learning aspects of pain.^{65 66} Fundamental to the biobehavioural perspective is the assertion that people learn to predict future events based on prior learning experiences and information processing. As such, patients' behaviours elicit responses from significant others, including healthcare professionals, which can reinforce both adaptive and maladaptive modes of thinking, feeling and behaving.⁶⁵ With this understanding, patients' pain-related cognitions and behaviours are of chief concern with respect to identifying factors that may contribute to the transition from acute post-op pain to chronic pain. In moving the science forward, we therefore give primacy to the cognitive-behavioural side of the global biobehavioural view of pain, as the conceptual premise for our primary objective. According to the fundamental tenets of the cognitive-behavioural perspective of pain^{65 66}: (A) behaviour is reciprocally determined by the person and environment, (B) people can learn more adaptive ways of thinking and behaving and (C) people are capable of and should be involved as active agents in the change of maladaptive thoughts, amenable to intervention.⁶⁵ Our focus therefore will be on the contribution of patients' pain-related beliefs and expectations, as follows:

Pain-related beliefs

Decades of work^{9 67–82} in the fields of post-op pain and anaesthesia has demonstrated that surgical patients have beliefs about pain and pain medication, which: (A) are based on incorrect information and (B) serve to block effective pain assessment and management. For example, one study found that among patients undergoing CABG

surgery (n=202), a majority (83%) reported that they would not voluntarily ask for pain medication when they needed it, although most reported unrelieved moderate-to-severe pain from post-op day 2 (80%) until day 5 (69%).⁶⁷ As of 2013, data indicate that this unfortunate scenario remains largely unchanged. Cogan *et al*⁸² found that among cardiac surgery patients (n=564), 36% believed that 'pain medication should be spared until the pain is very severe', 20% believed that 'good patients do not speak of their pain' and 31% believed it is 'very easy to become addicted to pain medication' while recovering from surgery. The particular role of these beliefs *per se* in the development of CPSP has yet to be examined; we will do so in this study using the Pain Barriers Questionnaire (PBQ) (validated in multiple populations).

Gender-based pain expectations

As with a number of fields in the health sciences, the study of sex and gender, as they relate to pain, is evolving. Our comprehensive review of risk factors for CPSP after cardiac surgery revealed that, thus far, investigation has been limited to the contribution of sex only as a risk factor. For the purposes of this study, we employ the following distinctions between sex and gender, set forth by Lips,⁸³ which have been adopted in a number of well-cited pain studies^{84–99}: sex: the biological distinction of being male or female; gender: learnt masculinity or femininity, related to socially-constructed roles and behaviours attributed to men and women in society.^{83 84}

Emerging evidence suggests that gender-based pain expectations defined as 'Sex-related stereotypic attributions about pain sensitivity, pain endurance, and willingness to report pain'⁸⁷ may lead to important differences in the experience of pain and related response. Robinson *et al* were among the first to investigate gender-based pain expectations, using the Gender Role Expectations of Pain Questionnaire (GREP).⁸⁷ Their study of pain cognitions in 156 men and 235 women found that men were perceived to be less willing to report pain than women, women were perceived to be more sensitive and less enduring of pain than men and that men rated their pain endurance as higher than average. Further testing of the GREP by Wise *et al*⁹⁴ found that after controlling for age, GREP scores accounted for 7%, 11% and 21% of the variance in pain threshold, tolerance and pain unpleasantness scores, respectively, for women (n=87) and men (n=61) exposed to thermal testing. A recent meta-analysis by Alabas *et al*,⁹¹ for example, examined the role of gender-related cognitions in the experience of pain.⁹¹ Pooling the results of six trials (406 men and 539 women), they found that those who considered themselves more masculine and less sensitive to pain, than the typical man, exhibited higher pain thresholds and tolerances in a variety of settings. Using the GREP, our study will be the first we know of to examine the role of gender-based pain expectations on the development of CPSP after cardiac surgery.

Health-related quality of life

Overwhelming evidence documents the deleterious impact of CPSP on health-related quality of life.^{6–31 50–62}

Cost of illness

We will examine the impact of CPSP on patient-level cost, calculated from a societal perspective, wherein all costs irrespective of payer are included thereby comprising private and public costs, using the Ambulatory Home Care Record. Data are available that indicate that from 20% to 30% of the occurrence of chronic pain is related to CPSP.^{98 99} Given the rates of cardiac surgery in Canada,^{4 5} literature has shown that CPSP contributes substantially to the \$22.2 billion in direct and indirect costs borne by cardiovascular interventions and services annually.¹⁵ With a view to comprehensive examination of the impact of CPSP, we will: (A) estimate the extra cost, expressed in healthcare costs, for patients with CPSP compared with those without and (B) estimate an incremental cost-effectiveness ratio, that is, the incremental cost for one additional quality-adjusted life year (QALY) gained, by virtue of cardiac surgery, among those who develop CPSP compared with those who do not. QALY is a preference-based utility measure of health-related quality of life as perceived by the patient.^{100 101} QALYs incorporate both length of life and quality of life into a single measure and are calculated by combining health-related quality of life measures with data on health state duration. As such, QALY is the gold standard measure of effectiveness recommended for economic evaluation and represents a universally comparable outcome measure. QALY will be derived from our Short Form-12 (SF-12) version 2 (SF-12v2) data.

Study objectives

Our primary objective is to examine the influence of pain-related beliefs and gender-based pain expectations on the development of chronic pain following cardiac surgery. Our secondary objectives are to: (A) examine the influence of pain-related beliefs and gender-based pain expectations on functional status and patient-level cost of illness following cardiac surgery; and (B) to determine the impact of CPSP on the QALY borne by cardiac surgery and the incremental cost for one additional QALY gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared with those who do not.

METHODS AND ANALYSIS

Design

This study is a substudy of the Vascular Events In Surgery patients cOhort evaluation - Cardiac Surgery study (<https://clinicaltrials.gov/ct2/show/NCT01842568>), examining 30-day all-cause mortality, myocardial injury and related complications following cardiac surgery in 15 000 participants. In this substudy, we propose to prospectively follow a cohort of patients who have undergone cardiac surgery for 1 year. Data on potential

predictors will be collected at baseline. The total follow-up period is 12 months, with pain, functional status and cost of illness-related data being collected at 6 months and 12 months following cardiac surgery.

Patient and public involvement

We collected patient testimonials to articulate the nature of the chronic pain problem following cardiac surgery from the patient perspective and establish the need for this study. Following the completion of the study, we will debrief the patient panel with the results of our findings.

Study population

The target population of 1250 cardiac surgery patients will be recruited from participating hospital sites in Canada, USA and Hong Kong. Patients eligible for our study will be undergoing a first-time cardiac surgery involving a median sternotomy, including CABG and all open heart procedures, such as valvular repairs/replacement. Eligible patients will also be able to read, speak and understand English and have a telephone allowing for follow-up. Patients will be ineligible if they: (A) have undergone previous cardiac surgery, thoracotomy or mastectomy, (B) are scheduled for an isolated pericardial window procedure (due to malignancy), pericardectomy, permanent pacemaker, or defibrillator implantation, (C) have a major cognitive disorder precluding participation, or (D) have a hearing impairment or speech impediment precluding telephone-based follow-up.

Cardiac surgery inpatients will be recruited in one of two ways: (1) from the hospital sites preoperative assessment clinic, if their surgery is prebooked, or (2) from the cardiac surgical ward, if they have been admitted to hospital via the hospital's emergency department or the heart investigation unit. A study nurse will obtain written, informed consent to participate among those willing and interested. The study enrolment period will conclude once the 1-year follow-up telephone interview is complete.

Data collection

Immediately following enrolment, standard baseline demographic, independent variable data (participants' age, sex, ethnicity, highest level of formal education, and marital and employment status) and data on baseline covariates (age and sex) will be collected by the study nurse via interview and chart audit. Postoperatively, the study nurse will collect data on surgical details via chart audit, and data on post-op day 3 cumulative analgesic dose and pain intensity scores via chart audit and participant interview, respectively. The study nurse will contact patients by phone at 30 days, and 6 and 12 months after surgery; the 30-day call will be for post-op pain monitoring, and the two subsequent calls will be for outcome assessment. Data on dependent variables will be measured at 6 months and 12 months following cardiac surgery. Table 1 outlines this visit schedule. The timing of this follow-up outcome measurement is in compliance with recommendations (2013) set forth by the Initiative

Table 1 Visit schedule

	Baseline	Postoperative day 3	Day 30	6 months	1 year
Pain Barriers Questionnaire	X				
Gender-based pain expectations	X				
Somatic Pre-Occupation and Coping	X				
State-Trait Anxiety Inventory	X				
Hospital Anxiety and Depression Scale (HADS)	X				
Short Form-12 (SF-12)	X		X	X	X
CPSP-related disability	X			X	X
Analgesic chart audit		X			
Brief Pain Inventory		X	X	X	X
Ambulatory Home Care Record				X	X

for Methods, Measurement, and Pain Assessment in Clinical Trials to standardise the timing of outcome assessment for prognostic studies of CPSP.¹⁰²

Dependent variables

Chronic postsurgical pain

The development of CPSP will be measured using a telephone structured interview protocol, defined as pain: (A) that developed after the surgical procedure, (B) is different from pain experienced prior to the procedure (eg, preoperative angina), (C) is not caused by other factors (eg, cancer recurrence and chronic infection), (D) is present for at least 2–3 months and (E) that interferes significantly with health-related quality of life.^{34–40}

If participants answer in the affirmative to each of these questions, it will be indicated that ‘Yes’ they have developed CPSP; otherwise, it will be indicated that ‘No’ they have not. Among those deemed to have developed CPSP (ie, ‘yes’) pain intensity, and its related interference with usual daily activities, will be measured via the Brief Pain Inventory-Short Form (BPI-SF).^{103–107} The BPI-SF includes four 11-point NRSs of pain intensity, which measure ‘average’, ‘least’ and ‘worst’ pain intensity in the past 24 hours, respectively, as well as pain intensity ‘now’ (0=no pain, 10=pain as bad as you can imagine). As is common to studies of CPSP^{28 29 62 67 108–113} (including cardiac surgery), participants will be asked for their ‘worst’ pain intensity rating both on rest and movement in the past 24 hours. The BPI-SF interference subscale^{103–107} will also be used, which measures the degree to which pain interferes with general activity, mood, walking, work, relations with others, sleep and enjoyment of life (NRS for each item; 0=does not interfere, 10=completely interferes). A total interference score is taken by calculating the sum of these seven items. The BPI-SF has strong psychometric properties with well-established reliability and validity across divergent surgical groups,^{29 103–117} including those reporting acute and chronic pain following cardiac surgery.^{28 29 62 67 112 113} The BPI-SF also contains supplemental items,^{103–106} for optional use (pain treatment and body diagram). Of these, only the body diagram will be used for descriptive purposes.

Functional status

Functional status will be measured with the SF-12v2), an established reliable and validated health status measure.¹¹⁸ It consists of 12 items taken from the Short Form 36 (SF-36), which is a widely accepted instrument that was developed from the Medical Outcomes Study.^{119–121} The SF-12v2 was developed to reduce respondent burden. It can be administered by telephone interview and consists of two scales that measure physical and mental health status. The SF-12v2 comprises eight domains, measured via eight subscales: (1) physical functioning; (2) role limitations due to physical problems; (3) role limitations due to emotional problems; (4) bodily pain; (5) general health; (6) vitality; (7) social functioning; and (8) mental health. Results may be expressed as physical component summary (PCS) and mental component summary scores. These scores range from 0 (worst) to 100 (best).¹¹⁸

Cost of illness

The Ambulatory and Home Care Record (AHCR)^{122–132} will be used to measure patient-level cost of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers, such as family members and friends. Items in the AHCR can be categorised as publicly financed care (ie, resources paid for by the public sector) or privately financed care (ie, all out-of-pocket payments, third party insurance payments and time costs incurred by caregiver). Face validity of the AHCR has been assessed by several healthcare providers, health economists and administrators who work in the field of ambulatory and home-based care.^{122 125} Reliability of the AHCR has been assessed via the level of agreement between self-reports of cost by cystic fibrosis care recipients and administrative data.¹²⁵ Moderate to almost perfect agreement was found between study participants’ responses on the AHCR and administrative data (kappa=0.41–1.00).¹²⁵ The AHCR has since been used to evaluate various conditions,^{124–132} including chronic cardiology patients who were interviewed over the phone.^{131 132} Additionally, the AHCR has been used to assess costs for an array of patients, including

the elderly, middle-aged adults and children.^{122–132} The AHCR has been used in telephone and face-to-face interviews as well as in mailed form; it has been translated into several languages.^{122–132}

Independent variables

Pain-related beliefs

Pain-related beliefs will be examined at baseline using the PBQ^{76 77} version II (PBQ-II)^{74 76–79 133}. The PBQ-II¹³⁴ includes 27 items divided into four subscales: erroneous beliefs regarding secondary effects of medication (12 items) and their harmful effects (six items), fatalism about the control of pain (three items) and attitudes regarding reporting pain to health professionals (six items). Each item is rated on a 0–5 scale (0: totally disagree; 5: totally agree). A total score and scores for each subscale can be calculated by taking the sum of the items. The PBQ-II has established validity, internal consistency and sensitivity to change^{113 135 136} and has recently been adapted and validated for use with cardiac surgical patients.¹¹³

Gender-based pain expectations

Gender-based pain expectations will be measured at baseline using the GREP. The GREP⁸⁷ measures stereotypic attributions regarding three constructs: pain endurance, pain sensitivity and willingness to report of pain. Each construct includes four 100 mm visual analogue scales regarding how women and men perceive themselves and the opposite sex, relative to: (A) their own sex and (B) the opposite sex with respect to how much pain can males/females endure, how sensitive to pain males/females are and how willing males/females are to report pain; respondents indicate their views on a 100 mm line anchored by 0 (far less) and 100 (far more). An average score is derived for each construct; greater scores indicate more stereotypical views. The GREP has now been used in multiple pain investigations.^{87 89 91–93 137 138} Test–retest reliability is acceptable across items⁸⁷ (0.53 to 0.93), and internal consistency reliability testing has demonstrated high correlations (–0.71 to –0.81) between individual items which assess opposite perceived gender roles (eg, typical masculine vs feminine orientation to pain endurance).⁸⁷

Covariates

We will control for the following demographic, clinical and surgical covariates: sex, age, BMI, diabetes mellitus, peripheral arterial disease, preoperative chronic pain and angina (Canadian Cardiovascular Society class), non-skeletonised internal thoracic artery harvest, re-sternotomy and operating time. Additional covariates include baseline functional status, anxiety and acute post-op pain.

Functional status

We will control for baseline functional status using the SF-12v2 PCS score.¹¹⁸

Baseline anxiety

We will control for anxiety at baseline using the Spielberger State-Trait Anxiety Inventory (STAI), a widely used,

well-validated anxiety measure.^{139 140} The STAI has 40 items that comprise two domains: the State (STAI-S) and Trait (STAI-T) score, both ranging from 20 to 80, with higher scores representing higher levels of anxiety. The STAI-S measures the transitional emotional status evoked by a stressful situation, such as surgery. The STAI-T score reflects enduring individual differences in the likelihood of anxiety.¹⁴¹ The STAI has been found reliable and valid among patients undergoing cardiac surgery (Cronbach's $\alpha=0.94$)¹⁴² and is commonly applied in studies capturing preoperative anxiety among cardiac surgery patients.^{143 144}

Acute post-op pain

Pain on post-op days 3 and 30 will be measured with the BPI. Cumulative 24 hours analgesic on post-op day 3, as an indication of analgesic dosing in hospital during recovery, will be determined via chart audit using a tool we have used in previous cardiac studies.^{28 62 67} Opioid dosage will be converted into parenteral morphine equivalents per day using standard dosage tables.^{28 62 67}

Sample size

The primary analysis for this study is the association of pain-related beliefs and gender-based pain expectations with CPSP at 6 months and 12 months while adjusting for a number of prespecified covariates. Therefore, sample size was calculated based on the methods used by Hsieh and colleagues¹⁴⁵ for multivariable logistic regression. In this validated method, the sample size for a simple logistic regression modelling a single independent variable X1 on the outcome is inflated by a variance inflation factor equal to $1 / (1 - \rho^2 \times 2 \dots xp)$, where $\rho^2 \times 2 \dots xp$ is equal to the proportion of the variance of X1 explained by the regression relationship with X2...Xp.¹⁴⁵ Additionally, sample size was inflated to account for the clustered nature of the data (ie, 6-month and 12-month measurements) by incorporating an additional design effect equivalent to $1 + (m - 1) \times \rho ICC$, where m is the number of measurements per cluster (ie, two time points) and ρICC represents the correlation of responses within clusters. A conservative scenario was assumed in which the correlation between the two follow-up measurements could be as high as 0.60, and the variance of the independent variables explained by covariates (ie, R^2) was 0.16, resulting in a requirement of 1250 participants to detect a significant change in the odds of post-op pain of 5% (ie, OR of 1.05). This calculation allows the prevalence of CPSP to be as low as 10% (as found in some previous studies). Should the prevalence of CPSP be higher, the correlation between measurements be smaller, or the variance explained in the independent variables be smaller, 1250 participants will provide >80% power.¹⁴⁵

Data analyses

Categorical data (eg, presence or absence of CPSP at 6 months and 1 year) will be summarised with frequencies and proportions. Continuous data (eg, functional disability scores) will be evaluated for normality using Shapiro-Wilk tests of normality and summarised using

measures of central tendency and dispersion (eg, means and SD for normally distributed factors and medians and IQRs for non-normally distributed data). Generalised estimating equations (GEEs) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6 months and 1 year while adjusting for prespecified covariates. GEE models account for the lack of independence in outcome measurements introduced by multiple measurements.¹⁴⁶ We will enter all prespecified variables in the model and retain them throughout the analysis. For each model, the inclusion of an interaction term between the two independent variables of interest (pain belief scale and gender-based pain expectations) will be guided by 95% CIs and likelihood ratio significance tests. Model diagnostics will consist of influential observation examination and Breslow-Day tests for goodness of fit.^{147 148} We will also assess for multicollinearity in our model via assessment of condition indices.^{147 148}

QALYs^{100 101} will be estimated by converting SF-12v2 data collected in the study to utility score using a validated algorithm.¹⁴⁹ After estimating QALYs, we will analyse it as a dependent variable using regression to estimate the difference in expected QALYs between the two groups (ie, those with CPSP vs those without). In addition, after calculating total cost from the AHCR, we will analyse it as a dependent variable using regression to estimate the difference in expected healthcare cost between the two groups (ie, patients with CPSP vs those without). Employing regression will allow for the adjustment of potential confounders. With a variety of different types of regression (ie, ordinary least squares and generalised linear models), we will explore the impact of various modelling assumptions. In addition, we will compare parametric and non-parametric CIs using bootstrapping. In theory, an ordinary least squares model produces unbiased estimates even if the data are skewed; however, different estimation methods (eg, generalised linear models) and different uncertainty methods (eg, non-parametric bootstrapping) will facilitate careful investigation of the impact that various assumptions have on our conclusions.^{150–153} The regression models will provide estimates of differences in QALYs and costs for participants who develop CPSP versus those who do not develop CPSP, which will allow us to calculate incremental cost for one QALY gained. A cost-effectiveness acceptability curve and 95% CI will be used to characterise the uncertainty of our findings.¹⁵³

Ethics and dissemination

Both integrated and end-of-grant dissemination strategies will be implemented. Study progress and results will be disseminated on CardiacPain.Net,¹⁵⁴ a web-based pain resource centre (<http://cardiacpain.onlinecjc.ca/>) linked to Elsevier's global online readership, featuring active knowledge 'push' mechanisms including e-banner advertising and opt-in email blasts. Final results will be

presented at international conferences and published in scientific journals.

Implications

CPSP is an important socioeconomic problem with well-documented deleterious consequences on functional status for cardiac patients. We aim to investigate putative psychological risk factors that could be targeted for preventative intervention. We will also examine the economic consequences of CPSP comprehensively, including the impact on QALYs, with no additional data collection required. This study may contribute towards reducing the risk and impact of CPSP after cardiac surgery.

Author affiliations

¹School of Nursing, McMaster University, Faculty of Health Sciences, Hamilton, Ontario, Canada

²Anesthesiology, Perioperative Medicine and Surgical Research Unit, Population Health Research Institute, Hamilton, Ontario, Canada

³Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

⁴Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

⁵Department of Psychology, York University, Toronto, Ontario, Canada

⁶Centre de recherche de Centre hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

⁷Department of Anesthesiology and Perioperative Medicine, Queen's University, Kingston, Ontario, Canada

⁸Department of Anesthesiology, Kingston General Hospital, Kingston, Ontario, Canada

⁹Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

¹⁰Department of Public Health Sciences, University of California, Davis, Davis, California, USA

¹¹School of Physical Therapy, Western University, London, Ontario, Canada

¹²College of Nursing, Florida State University, Tallahassee, Florida, USA

¹³Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada

¹⁴Department of Anesthesiology, David Geffen School of Medicine at University of California, Los Angeles, California, USA

¹⁵Department of Anesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, Hong Kong

¹⁶Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada

Contributors MHM, PJD, JWB, JCV, JKa, AL, RW, SP, HC, SLC, ND, HS and DNB contributed to the conception and design of the study. KB, JH, KG, DD-S and SH contribute to the acquisition of data; data analyses and interpretation will be conducted by MHM, JWB, PJD, SH, CO, PCC, SE, DNG, JH, WI, JKa, SI, JM, HC, GM, JCV, SSY, JP, IG, MTVC, MC, JW-W, KH-Q, AM. MHM, JB, JKH and PJD wrote the first draft of the protocol. JCV, JKa, AL, MC, RW, SP, KB, HS and JW-W revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published. The authors wish to thank our patient advisors for their testimonials, which served to establish the need for this study.

Funding This work is supported with funding from the Canadian Institutes of Health Research, #MOP-133714, The Hamilton Academic Health Sciences Organization, and the General Research Fund 14101414, Research Grant Council, Hong Kong SAR.

Competing interests MHM and PJD are members of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions, PJD has originated and grants he has written, he has received grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. PJD has participated in a consultancy advisory board meeting for Boehringer Ingelheim.

Patient consent Obtained.

Ethics approval This protocol has been approved by the responsible bodies at each of the hospital sites. Hamilton Integrated Research Ethics Board.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- Public Health Agency of Canada. Tracking heart disease and stroke in Canada 2009. <http://www.phac-aspc.gc.ca/publicat/2009/cvd-avc/index-eng.php> (accessed Nov 2017).
- Yusuf S, Reddy S, Ounpuu S, *et al*. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. *Circulation* 2001;104:2855–64.
- Svensden A. The current status of cardiovascular disease in Canada—a call to action. *Can J Cardiovasc Nurs* 2004;14:5–7.
- Roger VL, Go AS, Lloyd-Jones DM, *et al*. Heart disease and stroke statistics—2012 update: a report from the American heart association. *Circulation* 2012;125:e2–e220.
- Feindel CM. The current status of cardiac surgery workforce in Canada. 2010 http://www.royalcollege.ca/portal/pls/portal/PWEB_PORTAL.wwpob_page.show?_docname=509027.PDF.
- Bar-EI Y, Gilboa B, Unger N, *et al*. Skeletonized versus pedicled internal mammary artery: impact of surgical technique on post CABG surgery pain. *Eur J Cardiothorac Surg* 2005;27:1065–9.
- Bruce J, Drury N, Poobalan SA, *et al*. The prevalence of chronic chest and leg pain following cardiac surgery: a historical cohort study. *Pain* 2003;104:265–73.
- Eisenberg E, Pultorak Y, Pud D, *et al*. Prevalence and characteristics of post coronary artery bypass graft surgery pain (PCP). *Pain* 2001;92:11–17.
- Gjeilo KH, Klepstad P, Wahba A, *et al*. Chronic pain after cardiac surgery: a prospective study. *Acta Anaesthesiol Scand* 2010;54:70–8.
- Ho SC, Royse CF, Royse AG, *et al*. Persistent pain after cardiac surgery: an audit of high thoracic epidural and primary opioid analgesia therapies. *Anesth Analg* 2002;95:820–3.
- Jensen MK, Andersen C. Can chronic poststernotomy pain after cardiac valve replacement be reduced using thoracic epidural analgesia? *Acta Anaesthesiol Scand* 2004;48:871–4.
- Kalso E, Mennander S, Tasmuth T, *et al*. Chronic post-sternotomy pain. *Acta Anaesthesiol Scand* 2001;45:935–9.
- King KM, Parry M, Southern D, *et al*. Women's Recovery from Sternotomy-Extension (WREST-E) study: examining long-term pain and discomfort following sternotomy and their predictors. *Heart* 2008;94:493–7.
- Lahtinen P, Kokki H, Hynynen M. Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 2006;105:794–800.
- Mailis A, Umana M, Feindel CM. Anterior intercostal nerve damage after coronary artery bypass graft surgery with use of internal thoracic artery graft. *Ann Thorac Surg* 2000;69:1455–8.
- Meyerson J, Thelin S, Gordh T, *et al*. The incidence of chronic post-sternotomy pain after cardiac surgery—a prospective study. *Acta Anaesthesiol Scand* 2001;45:940–4.
- Steegeers MA, van de Luijckgarden A, Noyez L, *et al*. The role of angina pectoris in chronic pain after coronary artery bypass graft surgery. *J Pain* 2007;8:667–73.
- Taillefer MC, Carrier M, Bélisle S, *et al*. Prevalence, characteristics, and predictors of chronic nonanginal postoperative pain after a cardiac operation: a cross-sectional study. *J Thorac Cardiovasc Surg* 2006;131:1274–80.
- Ucak A, Onan B, Sen H, *et al*. The effects of gabapentin on acute and chronic postoperative pain after coronary artery bypass graft surgery. *J Cardiothorac Vasc Anesth* 2011;25:824–9.
- van Gulik L, Ahlers SJ, van de Garde EM, *et al*. Remifentanyl during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. *Br J Anaesth* 2012;109:616–22.
- van Gulik L, Janssen LH, Ahlers SJ, *et al*. Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur J Cardiothorac Surg* 2011;40:1309–13.
- Wiklund L, Johansson M, Bugge M, *et al*. Early outcome and graft patency in mammary artery grafting of left anterior descending artery with sternotomy or anterior minithoracotomy. *Ann Thorac Surg* 2000;70:79–83.
- Lee W, Yan YY, Jensen MP, *et al*. Predictors and patterns of chronic pain three months after cardiac surgery in Taiwan. *Pain Med* 2010;11:1849–58.
- Garland R, Frizelle FA, Dobbs BR, *et al*. A retrospective audit of long-term lower limb complications following leg vein harvesting for coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2003;23:950–5.
- Herlitz J, Brandrup-Wognsen G, Evander MH, *et al*. Symptoms of chest pain and dyspnoea during a period of 15 years after coronary artery bypass grafting. *Eur J Cardiothorac Surg* 2010;37:112–8.
- Momeni M, De Kock M, Lavand'homme P, *et al*. Abnormal sensations evoked over the chest and persistent peri-incisional chest pain after cardiac surgery. *Acta Anaesthesiol Belg* 2010;61:55–62.
- Onan B, Onan IS, Kilickan L, *et al*. Effects of epidural anesthesia on acute and chronic pain after coronary artery bypass grafting. *J Card Surg* 2013;28:248–53.
- Choinière M, Watt-Watson J, Victor JC, *et al*. Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 2014;186:E213–E223.
- Parry M, Watt-Watson J, Hodnett E, *et al*. Pain experiences of men and women after coronary artery bypass graft surgery. *J Cardiovasc Nurs* 2010;25:E9–E15.
- van Leersum NJ, van Leersum RL, Verwey HF, *et al*. Pain symptoms accompanying chronic poststernotomy pain: a pilot study. *Pain Med* 2010;11:1628–34.
- Routledge FS, Tsuyuki RT, Hervas-Malo M, *et al*. The influence of coronary artery bypass graft harvest site on women's pain, functional status, and health services utilization throughout the first post-operative year: a longitudinal study. *Int J Nurs Stud* 2009;46:1054–60.
- Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother* 2009;9:723–44.
- Macrae WA, Davies HTO, *et al*. Chronic postsurgical pain. In: Crombie IK, Croft PR, Linton SJ, LeResche L, Von Korf M, eds. *Epidemiology of pain*. Seattle: IASP Press, 1999:125–42.
- Kalso E, Perttunen K, Kaasinen S. Pain after thoracic surgery. *Acta Anaesthesiol Scand* 1992;36:96–100.
- Perttunen K, Tasmuth T, Kalso E. Chronic pain after thoracic surgery: a follow-up study. *Acta Anaesthesiol Scand* 1999;43:563–7.
- Jung BF, Ahrendt GM, Oaklander AL, *et al*. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 2003;104:1–13.
- Callesen T, Bech K, Kehlet H. Prospective study of chronic pain after groin hernia repair. *Br J Surg* 1999;86:1528–31.
- Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. *Anesthesiology* 2000;93:1123–33.
- Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? *Br J Anaesth* 2014;113:1–4.
- Weinrib AZ, Azam MA, Birnie KA, *et al*. The psychology of chronic post-surgical pain: new frontiers in risk factor identification, prevention and management. *Br J Pain* 2017;11:169–77.
- Moore R, Follette DM, Berkoff HA. Poststernotomy fractures and pain management in open cardiac surgery. *Chest* 1994;106:1339–42.
- Eng J, Wells FC. Morbidity following coronary artery revascularisation with the internal mammary artery. *Int J Cardiol* 1991;30:55–9.
- Conacher ID, Doig JC, Rivas L, *et al*. Intercostal neuralgia associated with internal mammary artery grafting. *Anaesthesia* 1993;48:1070–1.
- Defalque RJ, Bromley JJ. Poststernotomy neuralgia: a new pain syndrome. *Anesth Analg* 1989;69:81–2.
- Watts R, Davies R, Treasure T. Internal mammary artery grafting increases the incidence of shoulder girdle pain after cardiac surgery. *J Brit Heart* 1988;59:105–6.
- Wolf CJ, Salter M. Plasticity and pain. In: MacMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5 edn. Philadelphia: Elsevier Churchill Livingstone, 2006:91–105.
- Basbaum A, Bushnell MC, Devor M. Pain: basic mechanisms. In: Castro-Lopes J, Raja S, Schmelz M, *Pain 2008. An Updated Review Refresher Course Syllabus*. Glasgow: IASP Press, 2008:3–10.
- Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 1965;150:971–8.

49. Katz J, Rosenbloom BN, Fashler S. Chronic pain, psychopathology, and dsm-5 somatic symptom disorder. *Can J Psychiatry* 2015;60:160–7.
50. Markman PL, Rowland MA, Leong JY, et al. Skeletonized internal thoracic artery harvesting reduces chest wall dysesthesia after coronary bypass surgery. *J Thorac Cardiovasc Surg* 2010;139:674–9.
51. Gureje O, Von Korff M, Simon GE, et al. Persistent pain and well-being: a world health organization study in primary care. *JAMA* 1998;280:147–51.
52. Gureje O, Simon GE, Von Korff M. A cross-national study of the course of persistent pain in primary care. *Pain* 2001;92:195–200.
53. Blyth FM, March LM, Brnabic AJ, et al. Chronic pain in Australia: a prevalence study. *Pain* 2001;89:127–34.
54. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. *Pain* 2003;106:127–33.
55. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. *Arch Gen Psychiatry* 2003;60:39–47.
56. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
57. Ashburn MA, Staats PS. Management of chronic pain. *The Lancet* 1999;353:1865–9.
58. Fricker J. *Pain in Europe*: Mundipharma International Ltd. www.painineurope.com, 1–23. 2003.
59. Becker N, Sjögren P, Bech P, et al. Treatment outcome of chronic non-malignant pain patients managed in a danish multidisciplinary pain centre compared to general practice: a randomised controlled trial. *Pain* 2000;84:203–11.
60. Wilson KG, Mikail SF, D'Eon JL, et al. Alternative diagnostic criteria for major depressive disorder in patients with chronic pain. *Pain* 2001;91:227–34.
61. Mäntyselkä PT, Turunen JH, Ahonen RS, et al. Chronic pain and poor self-rated health. *JAMA* 2003;290:2435–42.
62. Watt-Watson J, Choinière CJ. *Prevalence characteristics and risk factors of persistent post-operative pain after cardiac surgery*. Montreal, Canada: The 13th International Association for the Study of Pain World Congress Proceedings, 2010:2956.
63. Gilron I, Vandenkerkhof E, Katz J, et al. Evaluating the association between acute and chronic pain after surgery: impact of pain measurement methods. *Clin J Pain* 2017;33:588–94.
64. Boodhwani M, Lam BK, Nathan HJ, et al. Skeletonized internal thoracic artery harvest reduces pain and dysesthesia and improves sternal perfusion after coronary artery bypass surgery: a randomized, double-blind, within-patient comparison. *Circulation* 2006;114:766–73.
65. Flor H, Turk DC. Cognitive and learning aspects. In: MacMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*. 5 edn. Philadelphia: Elsevier Churchill Livingstone, 2006:241–58.
66. Turk DC, Flor H. The cognitive-behavioural approach to pain management. In: McMahon S, Koltzenburg M, eds. *Wall & Melzack's textbook of pain*. London: Elsevier, 2006:339–48.
67. Watt-Watson J, Stevens B, Katz J, et al. Impact of preoperative education on pain outcomes after coronary artery bypass graft surgery. *Pain* 2004;109:73–85.
68. Gunnarsdottir S, Serlin RC, Ward S. Patient-related barriers to pain management: the icelandic Barriers Questionnaire II. *J Pain Symptom Manage* 2005;29:273–85.
69. Leegaard M, Nåden D, Fagermoen MS. Postoperative pain and self-management: women's experiences after cardiac surgery. *J Adv Nurs* 2008;63:476–85.
70. Lorentzen V, Hermansen IL, Botti M. A prospective analysis of pain experience, beliefs and attitudes, and pain management of a cohort of Danish surgical patients. *Eur J Pain* 2012;16:278–88.
71. Macrae WA. Chronic post-surgical pain: 10 years on. *Br J Anaesth* 2008;101:77–86.
72. McDonald DD, McNulty J, Erickson K, et al. Communicating pain and pain management needs after surgery. *Appl Nurs Res* 2000;13:70–5.
73. Murnion BP, Gnjdjic D, Hilmer SN. Prescription and administration of opioids to hospital in-patients, and barriers to effective use. *Pain Med* 2010;11:58–66.
74. Ward S, Gatwood J. Concerns about reporting pain and using analgesics. A comparison of persons with and without cancer. *Cancer Nurs* 1994;17:200–6.
75. Watt-Watson J, Stevens B, Garfinkel P, et al. Relationship between nurses' pain knowledge and pain management outcomes for their postoperative cardiac patients. *J Adv Nurs* 2001;36:535–45.
76. Ward SE, Berry PE, Misiewicz H. Concerns about analgesics among patients and family caregivers in a hospice setting. *Res Nurs Health* 1996;19:205–11.
77. Ward S, Donovan HS, Owen B, et al. An individualized intervention to overcome patient-related barriers to pain management in women with gynecologic cancers. *Res Nurs Health* 2000;23:393–405.
78. Ward SE, Goldberg N, Miller-McCauley V, et al. Patient-related barriers to management of cancer pain. *Pain* 1993;52:319–24.
79. Ward SE, Hernandez L. Patient-related barriers to management of cancer pain in Puerto Rico. *Pain* 1994;58:233–8.
80. Watt-Watson J, Garfinkel P, Gallop R, et al. The impact of nurses' empathic responses on patients' pain management in acute care. *Nurs Res* 2000;49:191–200.
81. Watt-Watson J, Pain MA. In: Watt-Watson J, Donovan M, *Pain management: Nursing perspective*. St. Louis: Mosby, 1992:36–58.
82. Cogan J, Ouimette MF, Vargas-Schaffer G, et al. Patient attitudes and beliefs regarding pain medication after cardiac surgery: barriers to adequate pain management. *Pain Manag Nurs* 2014;15:574–9.
83. Lips HM. *Sex and Gender: An Introduction*. Mountain View, CA: Mayfield, 1993.
84. Tolver MA, Strandfelt P, Rosenberg J, et al. Female gender is a risk factor for pain, discomfort, and fatigue after laparoscopic groin hernia repair. *Hernia* 2013;17:321–7.
85. Uchiyama K, Kawai M, Tani M, et al. Gender differences in postoperative pain after laparoscopic cholecystectomy. *Surg Endosc* 2006;20:448–51.
86. Campesi I, Fois M, Franconi F. Sex and gender aspects in anesthetics and pain medication. *Handb Exp Pharmacol* 2012;214:265–78.
87. Robinson ME, Riley JL, Myers CD, et al. Gender role expectations of pain: relationship to sex differences in pain. *J Pain* 2001;2:251–7.
88. Hunt K, Adamson J, Hewitt C, et al. Do women consult more than men? A review of gender and consultation for back pain and headache. *J Health Serv Res Policy* 2011;16:108–17.
89. Robinson ME, Wise EA, Gagnon C, et al. Influences of gender role and anxiety on sex differences in temporal summation of pain. *J Pain* 2004;5:77–82.
90. Soetanto AL, Chung JW, Wong TK. Gender differences in pain perception: a signal detection theory approach. *Acta Anaesthesiol Taiwan* 2004;42:15–22.
91. Alabas OA, Tashani OA, Tabasam G, et al. Gender role affects experimental pain responses: a systematic review with meta-analysis. *Eur J Pain* 2012;16:1211–23.
92. Defrin R, Shramm L, Eli I. Gender role expectations of pain is associated with pain tolerance limit but not with pain threshold. *Pain* 2009;145:230–6.
93. Defrin R, Eli I, Pud D. Interactions among sex, ethnicity, religion, and gender role expectations of pain. *Gen Med* 2011;8:172–83.
94. Wise EA, Price DD, Myers CD, et al. Gender role expectations of pain: relationship to experimental pain perception. *Pain* 2002;96:335–42.
95. Wandner LD, Scipio CD, Hirsh AT, et al. The perception of pain in others: how gender, race, and age influence pain expectations. *J Pain* 2012;13:220–7.
96. Alabas OA, Tashani OA, Johnson MI. Gender role expectations of pain mediate sex differences in cold pain responses in healthy Libyans. *Eur J Pain* 2012;16:300–11.
97. Robinson ME, Gagnon CM, Riley JL, et al. Altering gender role expectations: effects on pain tolerance, pain threshold, and pain ratings. *J Pain* 2003;4:284–8.
98. Semple T. Post-surgical pain syndromes the medical insurance group. 2010 www.miga.com.au/riskresources/library/10RRAR07.pdf.
99. Davies HTO, Crombie IK, Macrae WA, et al. Pain clinic patients in northern britain. *Pain Clin* 1992;5:129–35.
100. Gold M, Siegel J, Russell L, et al. *Cost-effectiveness in health and medicine*. New York: Oxford University Press, 1996.
101. Drummond M, Sculpher M, Torrance G, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. New York: Oxford University Press, 2005.
102. VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. *Clin J Pain* 2013;29:2–8.
103. Cleeland C. Pain assessment in cancer. Osoba D, *Effect of cancer on quality of life*. Florida: CRC Press, 1999:293–305.
104. Cleeland C. *The Brief Pain Inventory user guide*. Houston, Texas: M. D Anderson 2009, Cancer Centre.
105. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994;23:129–38.

106. Cleeland CS, Syrjala KL. How to assess cancer pain. In: Turk DC, Melzack R, eds. *Handbook of pain assessment*. New York, NY: Guilford, 1992.
107. Tittle MB, McMillan SC, Hagan S. Validating the brief pain inventory for use with surgical patients with cancer. *Oncol Nurs Forum* 2003;30:325–30.
108. Watt-Watson J, Chung F, Chan VW, et al. Pain management following discharge after ambulatory same-day surgery. *J Nurs Manag* 2004;12:153–61.
109. Wilson R. *A randomized control trial of an individualized preoperative education intervention for symptom management following total knee arthroplasty* (Doctoral dissertation: University of Toronto, 2011).
110. Mendoza T, Mayne T, Rublee D, et al. Reliability and validity of a modified brief pain inventory short form in patients with osteoarthritis. *Eur J Pain* 2006;10:353–61.
111. Ochroch EA, Gottschalk A, Augoustides JG, et al. Pain and physical function are similar following axillary, muscle-sparing vs posterolateral thoracotomy. *Chest* 2005;128:2664–70.
112. Gjeilo KH, Stenseth R, Wahba A, et al. Validation of the brief pain inventory in patients six months after cardiac surgery. *J Pain Symptom Manage* 2007;34:648–56.
113. Martorella G, Côté J, Racine M, et al. Web-based nursing intervention for self-management of pain after cardiac surgery: pilot randomized controlled trial. *J Med Internet Res* 2012;14:e177.
114. Klepstad P, Loge JH, Borchgrevink PC, et al. The Norwegian brief pain inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage* 2002;24:517–25.
115. Ochroch EA, Gottschalk A, Troxel AB, et al. Women suffer more short and long-term pain than men after major thoracotomy. *Clin J Pain* 2006;22:491–8.
116. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113(1-2):9–19.
117. Larue F, Colleau SM, Brasseur L, et al. Multicentre study of cancer pain and its treatment in France. *BMJ* 1995;310:1034–7.
118. Ware J, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33.
119. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
120. McHorney CA, Ware JE, Lu JF, et al. The MOS 36-item Short-Form Health Survey (SF-36): III. Tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Med Care* 1994;32:40–66.
121. Ware JE. *SF-36 Physical & Mental Health Summary Scales: A User's Manual*. Lincoln, RI: Quality Metric Inc, 1997.
122. Guerriere DN, Ungar WJ, Corey M, et al. Evaluation of the ambulatory and home care record: Agreement between self-reports and administrative data. *Int J Technol Assess Health Care* 2006;22:203–10.
123. Stevens B, Guerriere D, McKeever P, et al. Economics of home vs. hospital breastfeeding support for newborns. *J Adv Nurs* 2006;53:233–43.
124. Drummond MF, O'Brien B, Stoddart GL, et al. *Methods for the Economic Evaluation of Health Care Programmes*. Toronto: Oxford University Press, 1997.
125. Guerriere DN, Tullis E, Ungar WJ, et al. Economic burden of ambulatory and home-based care for adults with cystic fibrosis. *Treat Respir Med* 2006;5:351–9.
126. Guerriere DN, Wong AY, Croxford R, et al. Costs and determinants of privately financed home-based health care in Ontario, Canada. *Health Soc Care Community* 2008;16:126–36.
127. Guerriere DN, Tranmer JE, Ungar WJ, et al. Valuing care recipient and family caregiver time: a comparison of methods. *Int J Technol Assess Health Care* 2008;24:52–9.
128. Guerriere DN, Choinière M, Dion D, et al. The Canadian STOP-PAIN project - Part 2: What is the cost of pain for patients on waitlists of multidisciplinary pain treatment facilities? *Can J Anaesth* 2010;57:549–58.
129. Guerriere DN, Zagorski B, Fassbender K, et al. Cost variations in ambulatory and home-based palliative care. *Palliat Med* 2010;24:523–32.
130. Leong VW, Guerriere DN, Croxford R, et al. The magnitude, share and determinants of private costs incurred by clients (and their caregivers) of in-home publicly financed care. *Healthc Policy* 2007;3:141–e159.
131. McGillion MH, Watt-Watson J, Stevens B, et al. Randomized controlled trial of a psychoeducation program for the self-management of chronic cardiac pain. *J Pain Symptom Manage* 2008;36:126–40.
132. McGillion MH, Croxford R, Watt-Watson J, et al. Cost of illness for chronic stable angina patients enrolled in a self-management education trial. *Can J Cardiol* 2008;24:759–64.
133. Ward SE, Carlson-Dakes K, Hughes SH, et al. The impact on quality of life of patient-related barriers to pain management. *Res Nurs Health* 1998;21:405–13.
134. Gunnarsdottir S, Donovan HS, Serlin RC, et al. Patient-related barriers to pain management: the Barriers Questionnaire II (BQ-II). *Pain* 2002;99:385–96.
135. Griffey D. Questionnaire translation and questionnaire validation: are they the same? *Proceedings of the Annual Meeting of the American Association of Applied Linguistics*. St Louis: MO URL, 2001.
136. Racine M, Tousignant-Lafamme Y, Kloda LA, et al. A systematic literature review of 10 years of research on sex/gender and pain perception - part 2: do biopsychosocial factors alter pain sensitivity differently in women and men? *Pain* 2012;153:619–35.
137. Chapman CR. Psychological aspects of pain patient treatment. *Arch Surg* 1977;112:767–72.
138. Scott LE, Clum GA, Peoples JB. Preoperative predictors of postoperative pain. *Pain* 1983;15:283–93.
139. Spielberger CD, Grambow SC, Machado C, et al. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, 1983.
140. Spielberger CD, Gorsuch A, Lushane R, et al. *Manual for the State-Trait Anxiety Inventory*. Palo Alto, California: Consulting Psychologists Press, 1970.
141. Cserép Z, Losoncz E, Balog P, et al. The impact of preoperative anxiety and education level on long-term mortality after cardiac surgery. *J Cardiothorac Surg* 2012;7:86.
142. Cserép Z, Balog P, Székely J, et al. Psychosocial factors and major adverse cardiac and cerebrovascular events after cardiac surgery. *Interact Cardiovasc Thorac Surg* 2010;11:567–72.
143. Detroyer E, Dobbels F, Verfaillie E, et al. Is preoperative anxiety and depression associated with onset of delirium after cardiac surgery in older patients? A prospective cohort study. *J Am Geriatr Soc* 2008;56:2278–84.
144. Székely A, Balog P, Benkő E, et al. Anxiety predicts mortality and morbidity after coronary artery and valve surgery--a 4-year follow-up study. *Psychosom Med* 2007;69:625–31.
145. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med* 1998;17:1623–34.
146. Hubbard AE, Ahern J, Fleischer NL, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. *Epidemiology* 2010;21:467–74.
147. Harrell FE. *Regression modeling Strategie*. New York: Springer, 2006.
148. Babyak MA. What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. *Psychosom Med* 2004;66:411–21.
149. Brazier J, Rowen D, Hanmer J. Revised SF-6D scoring programmes: A summary of improvements. *PRO newsletter* 2008;40:14–15.
150. Briggs A, Nixon R, Dixon S, et al. Parametric modelling of cost data: some simulation evidence. *Health Econ* 2005;14:421–8.
151. Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy* 2004;9:197–204.
152. Glick HA, Doshi JA, Sonnad SS, et al. *Economic evaluation in clinical trials*: OUP Oxford, 2014.
153. Hoch JS, Rockx MA, Krahn AD. Using the net benefit regression framework to construct cost-effectiveness acceptability curves: an example using data from a trial of external loop recorders versus Holter monitoring for ambulatory monitoring of "community acquired" syncope. *BMC Health Serv Res* 2006;6:68.
154. Arthur MM. No amount of pain is satisfactory: New perspectives on persistent cardiac pain. *Can J Cardiol* 2012;28:2.