Cognitive and psychological problems after total joint replacement in older adults.

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Abstract

Total joint replacement (TJR) of the hip or knee is a major elective procedure that is frequently performed in older adults to treat end-stage osteoarthritis. It is generally considered to be a highly successful procedure because it significantly reduces the pain and disability caused by severe arthritis, and allows people to resume many of their everyday activities. However, there is also research to suggest that older patients may be susceptible to cognitive and psychological problems following TJR.

Research investigating cognitive and psychological outcomes following TJR has provided mixed results, making it difficult to draw conclusions to inform clinical practice. While some studies have reported evidence of postoperative cognitive dysfunction (POCD) after TJR, others have not. Similarly, the reported rates of delirium after TJR have varied enormously (0% to 82%). In addition, estimates of the prevalence of clinically significant cases of depression and anxiety among TJR patients range from very high (i.e., 85-95%) to rates that are comparable to the general population. It is also unclear whether TJR has an impact on the levels of depression and anxiety that are reported by patients.

The current thesis examined the cognitive and psychological outcomes of persons undergoing TJR surgery in order to clarify the risk of these problems in this patient population. To this end, three meta-analyses (Chapters 3-5) were conducted to evaluate the risk of cognitive and psychological problems following TJR: one examined POCD, another delirium, and one depression and anxiety. Lastly, a clinical study was conducted (Chapter 6) to address the outstanding issues within the POCD literature revealed by these reviews.

Study 1 meta-analysed research that examined cognition pre- and post TJR. Data were categorised according to the cognitive domain that was assessed (e.g. memory, attention, executive function), follow-up interval (pre-discharge, 3 to 6 months post-

surgery) and study design (single TJR group repeated measures, TJR and Control group repeated measures). Unfortunately, the incidence of POCD could not be determined because the studies did not use comparable definitions of POCD. Furthermore, limited conclusions could be drawn, largely because practice effects were generally not adequately controlled for. Overall, this meta-analysis revealed the need for methodologically rigorous research that controls for repeat testing confounds and uses a theoretically and statistically defensible definition of cognitive decline to investigate the incidence and severity of POCD after TJR.

The second meta-analysis (Study 2) investigated the incidence of delirium after TJR, and whether differences in sample characteristics (e.g. hip vs knee, general vs regional anaesthesia) and study methodology (e.g. measure, assessment interval) contributed to the variability in the incidence rates reported by different studies. Delirium was found to occur in approximately one in six patients following TJR, but the variability in findings proved difficult to explain.

Study 3 meta-analysed the research that examined depression and anxiety symptoms pre- and post-TJR. This study examined the prevalence of clinically significant levels of depression and anxiety in TJR patients, and changes in these symptoms pre- to post-surgery. Data were grouped and analysed according to the length follow-up interval. Although only limited data were available, a high proportion of TJR patients appeared to experience clinically significant levels of depression and anxiety pre- and early post-surgery. Modest decreases in symptoms were observed after surgery, but were unlikely to reflect clinically significant change. Once again, this study highlighted the fact that few studies have used a control group.

Lastly, a clinical study (Study 4) was designed to overcome the limitations in previous research identified in Study 1 by including a control group and using standardised regression-based statistical methodology to reduce the confounding effects of repeat testing (practice effects, measurement error and regression to the mean) and to provide a statistically defensible definition of POCD. In addition, this study investigated whether POCD was related to cognitive reserve, which refers to individual differences in cognitive abilities that may protective against brain damage. Cognitive reserve has often been used to explain the lack of a clear relationship between brain pathology and the resulting symptoms, but has not yet been investigated in the context of POCD after TJR.

TJR and matched healthy control groups were recruited, and cognitive functioning was assessed using a battery of tests both pre- and post-surgery (6 months). Other variables that may have affected cognitive performance were also assessed (e.g. demographics, medical history, pain, psychological distress). This study found minimal evidence of POCD six months after TJR, with patients only experiencing significant decline in their performance on a single test. Although preliminary, this suggests that patients who undergo TJR have good cognitive outcomes post-surgery. Although at odds with the findings of many previous studies, it highlights the importance of controlling for repeated testing by using a control group and appropriate statistical techniques (standardised regression-based statistics).

Whether cognitive reserve was protective against POCD could only be explored to a limited degree because TJR patients only showed greater pre- to post-surgery decline on one task when compared to controls. Although cognitive reserve and performance on this task were not related, reserve predicted cognitive change among those TJR patients achieved the greatest improvement and greatest decline pre- to post-surgery, suggesting that cognitive reserve is related to better cognitive recovery post-surgery among a subset

of patients. It remains to be seen whether cognitive reserve would better predict POCD in a sample with more pronounced cognitive dysfunction.

Overall, this thesis provides a summary of the literature to date on cognitive and psychological outcomes after TJR in the elderly. In addition, this thesis has addressed some outstanding questions that remain regarding POCD. The clinical implications of these findings for patients who undergo TJR are discussed, and recommendations for future research are made.

Declaration

I, Julia Scott, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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Published works

Chapter 3: Study 1

Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2014). Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: A meta-analysis. *Journal of Arthroplasty, 29,* 261-267. doi:10.1016/j.arth.2013.06.007.

Chapter 4: Study 2

Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2015). Incidence of delirium following total joint replacement in older adults: A meta-analysis. *General Hospital Psychiatry, 37,* 223-229. doi:10.1016/j.genhosppsych.2015.02.004.

Chapter 5: Study 3

Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2016). Depression and anxiety after total joint replacement among older adults: a meta-analysis. *Aging and Mental Health, 20*, 1243-1242. doi:10.1080/13607863.2015.1072801.

Chapter 6: Study 4

Scott, J. E., Mathias, J. L., Kneebone, A. C., & Krishnan, J. (2016). Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients. *Journal of Clinical and Experimental Neuropsychology, In Press.* doi:10.1080/13803395.2016.1233940.

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Chapter 1. Cognitive and Psychological Problems in Patients who Undergo Total Joint Replacement

Total Joint Replacement in an Ageing Population

It is well documented that Australians are living longer than previous generations and this trend is expected to continue (Australian Bureau of Statistics, 2011b; Australian Institute of Health and Welfare, 2014; Healy, 2004). Over the last two decades, those aged 65 and over have increased from 11.8% to 14.7% of the population, and the proportion of people aged 85 and over has nearly doubled to 1.9% (Australian Bureau of Statistics, 2014). In addition, older adults are generally healthier and more active in their later years, compared to previous generations (Healy, 2004). This improved quality of life is partially due to changes in lifestyle factors that influence health, such as better nutrition and sanitation (Faria, 2002) and reduced rates of smoking (Australian Bureau of Statistics, 2011b; Mathers, Stevens, Boerma, White, & Tobias, 2014). Advances in medical care have additionally improved the management and treatment of chronic illnesses, such as cardiovascular disease, diabetes, cancer and arthritis (Mathers et al., 2014).

In particular, many major elective surgery procedures have been refined, reducing the risks associated with these procedures and maximising patient quality of life (Mathers et al., 2014). One example of such a procedure is 'total joint replacement' (also referred to as 'total joint arthroplasty') of the hip or the knee, which is frequently used to treat painful joint conditions that cause significant disability. Whereas total hip replacement involves the replacement of the femoral (neck and ball of the hip joint) and acetabular articular surfaces (hip socket; Australian Orthopaedic Association National Joint Replacement Registry, 2014a), total knee replacement involves the replacement of the entire

femorotibial articulation (knee joint) and sometimes the patella (kneecap; Australian Orthopaedic Association National Joint Replacement Registry, 2014b). Total joint replacement (TJR) may use cemented implants, which are fixed to the bone using surgical cement, or cementless (press-fixed) implants, which are held in place by the bone growing into the dimpled surface of the prosthesis (Harris & Sledge, 1990a, 1990b). Hybrid implants, on the other hand, involve a combination of the two, with a hybrid hip replacement using a cemented femoral stem prosthesis together with a cementless acetabular cup prosthesis (Pennington et al., 2013), and a hybrid knee replacement using a cementless femoral component and cemented tibial and patella components (Manner, 2016).

The majority of Australian patients who undergo TJR are older adults: approximately 87% and 93% of total hip and knee patients, respectively, are aged over 55; many of whom are female (Australian Orthopaedic Association National Joint Replacement Registry, 2015). Patients who undergo TJR generally spend three to five days in hospital after their surgery, but may stay for as little as two days (Kehlet, 2013,) or longer than one week if complications arise or the patient is slower to mobilise. TJR procedures typically take between 1-2 hours and are performed under general or regional anaesthesia, or a combination of both (Hill et al., 2008). Mobilisation and physiotherapy usually begin as soon as possible, often the day after surgery (Foran, 2011a, 2011b). Patients normally experience significant recovery by three months post-surgery (Holt, 2015) and full recovery usually occurs by six to twelve months (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2013).

TJR procedures have been refined over the decades to minimise risks and increase benefits and cost-effectiveness (Learmonth, Young, & Rorabeck, 2007). For example, whereas patients were previously in hospital for an average of ten days (Harris &

Sledge, 1990a), admissions are now much shorter (Kehlet, 2013). In addition, patients are now usually mobilised earlier and experience a faster recovery (Wellman, Murphy, Gulcynski, & Murphy, 2011). Furthermore, revision and complication rates have been reduced substantially (Learmonth et al., 2007). Minimally invasive approaches to surgery and computer navigation techniques, which improve the accuracy of bone cuts and implant placement, have also been developed (Wong, Khan, Chimutengwende-Gordon, & Dowd, 2011).

An increase in demand for, and improvements in, these surgical procedures have meant that the number of TJRs performed in Australia has risen dramatically. Indeed, the number of total hip replacements has increased by more than 600% since 2000, with over 44,000 procedures being conducted in 2015 alone (Australian Orthopaedic Association National Joint Replacement Registry, 2016a). Similarly, the number of knee replacements performed has increased in excess of 900% since 2000, with over 57,000 reported in 2015 (Australian Orthopaedic Association National Joint Replacement Registry, 2016b).

Although TJR can be used to treat multiple painful joint-related illnesses, the majority of procedures are used as a last-resort treatment for end-stage osteoarthritis. In 2015, a primary diagnosis of osteoarthritis accounted for approximately 89% of total hip replacements and 98% of total knee replacements (Australian Orthopaedic Association National Joint Replacement Registry, 2015). Osteoarthritis occurs when the cartilage cushioning within joints disintegrates, causing the joint to become painful and stiff. It is thought to be one of the most disabling chronic medical conditions (Arya & Jain, 2013; Corti & Rigon, 2003) and severely restricts everyday activity, such as driving, climbing stairs, and even walking (Corti & Rigon, 2003). Furthermore, osteoarthritis is extremely common; with approximately one quarter of adults over the age of 65, and one third of adults aged over 75, having this diagnosis (Australian Bureau of Statistics, 2011a). These

rates are predicted to increase due to the ageing population and a rise in obesity (Arya & Jain, 2013). Ultimately, the aim of TJR in the treatment of osteoarthritis is to provide patients with a functional joint that allows them to undertake everyday activities with substantially less pain (Harris & Sledge, 1990a, 1990b).

TJR procedures are considered to be among the most successful of all surgeries (Foran, 2011a, 2011b; Talmo, Robbins, & Bono, 2010), because they provide substantial improvements in pain and physical functioning (Ethgen, Bruyere, Richy, Dardennes, & Reginster, 2004), often returning levels that are comparable to their healthy peers (Wiklund & B., 1991). Major complications - such as myocardial infarction, pulmonary embolism, deep vein thrombosis and death - are rare, occurring at the rate of 0.4%, 0.7%, 1.5% and 0.5%, respectively, within 30 days of surgery (Wood et al., 2002). Furthermore, few patients who undergo TJR require surgical revision of their joint as a consequence of complications (Labek, Thaler, Janda, Agreiter, & Stockl, 2011). TJR is also a highly cost-effective treatment for patients of all ages and is associated with reduced lifetime health care costs, when compared to non-surgical treatments (Fordham, Skinner, Wang, & Nolan, 2012; Losina et al., 2009; Saleh, Wood, Gafni, & Gross, 1997). Therefore TJR offers substantial benefits to patient health and reduces the economic disease-burden to the health care sector.

As patients who undergo TJR are a large and growing population, optimal outcomes are of great clinical importance. Although research on the procedure, itself, is generally positive regarding the surgical benefits, there is less consensus about the impact of this surgery on some non-surgical outcomes. Specifically, research has reported that patients may experience cognitive problems after TJR, such as postoperative cognitive dysfunction (Evered, Scott, Silbert, & Maruff, 2011; Koch et al., 2007) and delirium (Contín, Perez-Jara, Alonso-Contín, Enguix, & Ramos, 2005; Kinjo, Lim, Sands, Bozic, &

Leung, 2012). In addition, patients may experience clinically significant levels of depression and anxiety, and the impact of TJR on these symptoms remains unclear (Duivenvoorden et al., 2013).

Postoperative Cognitive Dysfunction

Postoperative cognitive dysfunction (POCD) is a cognitive disorder that is common in older adults (Berger et al., 2015). It generally develops weeks or months after surgery (Monk & Price, 2011), and may manifest either as a marked deficit in one or two cognitive domains, or as more a global cognitive deficit (Deiner & Silverstein, 2009). The cognitive domains typically affected include memory, perception, attention, processing speed and executive function (Deiner & Silverstein, 2009; Krenk, Rasmussen, & Kehlet, 2010). Some patients with POCD experience subtle cognitive deficits, whereas others experience more substantial incapacity (Monk & Price, 2011). POCD is distinct from other neurocognitive disorders, such as dementia, because the cognitive problems develop as a direct consequence of surgery and are potentially reversible (Russell-Babin & Miley, 2013). Furthermore, POCD is distinct from delirium, which is a disturbance in attention and awareness that fluctuates throughout the day (Deiner & Silverstein, 2009).

POCD can be difficult to diagnose within a clinical setting for several reasons. First, POCD may be subtle and only perceptible to the patient and a close family member. Consequently it is often missed by treating clinicians (Shoair et al., 2015). Second, POCD may only become apparent once the patient has returned to their pre-operative employment, hobbies, and responsibilities (Tomaszewski, 2014), which may not occur until weeks or months after their surgery. Lastly, POCD is best diagnosed by comparing a patient's postoperative cognitive performance with their pre-operative performance

(Grape, Ravussin, Rossi, Kern, & Steiner, 2012). This allows for their postoperative cognition to be considered relative to their premorbid ability, rather than against a universal standard. However, pre-operative testing is not common and often not possible in a clinical setting, especially in cases of emergency surgery (Berger et al., 2015).

A number of patient groups are at particular risk of POCD. These include people undergoing emergency surgery, such as those with a hip fracture (Gruber Baldini et al., 2003; Papadopoulos G., Liarmakopoulou A., Korre M., & Beris, 2012) or in intensive care, as well as high-risk elective surgery patients, such as those undergoing coronary angiography, coronary artery bypass graft surgery (Evered et al., 2011) and intra-abdominal/thoracic surgery (Monk et al., 2008). It has also been found that patients who undergo TJR may develop POCD (Deo, West, Butcher, & Lewis, 2011; Salazar et al., 2011), with the rates reportedly varying from 16% to 45% (Evered et al., 2011; Koch et al., 2007).

Potential causes of postoperative cognitive dysfunction after total joint replacement

The potential causes of POCD following TJR remain controversial. General anaesthesia has been suggested to be a contributing factor; however, research has consistently failed to find a relationship between POCD and the use of general versus regional anaesthesia in TJR samples (Evered et al., 2011; Jones et al., 1990; Nielson et al., 1990). Postoperative analgesia has also been investigated more generally in the context of POCD in elderly surgical patients, although a review of the literature found that results were inconsistent and no firm conclusions could be drawn (Fong, Sands, & Leung, 2006). More recently, it has been suggested that endothelial dysfunction, caused by an

inflammatory cascade that is triggered by surgical insult, may contribute to POCD (Riedel, 2014), however this is yet to be explored among TJR samples.

Cerebral microemboli have also been explored as a possible mechanism for the development of POCD after elective cardiovascular surgery (Funder, Steinmetz, & Rasmussen, 2009) and TJR (Rodriguez et al., 2005). Microemboli consist of tiny particles of fat, bone marrow, air or surgical cement that are released into the bloodstream during surgery (Koessler & Pitto, 2002). During hip replacement, microemboli may be released during insertion of a cemented femoral component or immediately after relocation of the hip joint (Koessler & Pitto, 2002) and, during knee replacement, they may be released after the tourniquet is released (Sulek, Davies, Enneking, Gearen, & Lobato, 1999). Upon entry into the bloodstream, these microemboli can travel to the brain via a patent foramen ovale (i.e. hole between the upper chambers of the heart) or via transpulmonary passage (Koessler & Pitto, 2002; Sulek et al., 1999). The presence of cerebral microemboli has been assessed using intraoperative transcranial doppler ultrasonography (Silbert, 2014). Microemboli appear to be common after TJR and have been reported in 23% to 100% of hip replacement patients (Edmonds, Barbut, Hager, & Sharrock, 2000; Gray, Torrens, Howie, Christie, & Robinson, 2008; Koch et al., 2007; Patel, Stygall, Harrington, Newman, & Haddad, 2010; Riding et al., 2004), and between 38% to 100% of knee replacement patients (Koch et al., 2007; Patel et al., 2010; Riding et al., 2004; Rodriguez et al., 2005; Sulek et al., 1999).

It remains unclear whether cerebral microemboli are associated with the development of POCD. A systematic review of research examining cardiopulmonary bypass surgery reported that the majority of well-designed studies found no link between microemboli and POCD (Kruis, Vlasveld, & Van Dijk, 2010). However, the authors also stated that, due to serious limitations in the studies, it was not possible to conclusively

determine whether or not such a relationship exists. Although fewer studies have investigated this relationship in TJR samples, at least three failed to find a relationship (Gray et al., 2008; Koch et al., 2007; Rodriguez et al., 2005). Notably, these studies were limited by their small sample size (*N* ranged from 20 to 29), which reduced their statistical power.

Impact of postoperative cognitive dysfunction on outcomes after surgery

The impact of POCD on post-surgical outcomes in patients who undergo TJR has yet to be investigated. This appears to be a notable gap in the literature because comparable research with patients who undergo coronary artery bypass graft surgery suggest that the development of POCD is associated with poorer quality of life, greater limitations from their cardiac symptoms and greater depression at one year post-surgery, even after controlling for baseline quality of life, age, gender and medical comorbidities (Phillips-Bute et al., 2006). POCD is also associated with an increased risk of mortality in non-cardiac surgery patients (Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009).

Furthermore, POCD appears to have financial consequences for patients and the broader community. Specifically, the development of POCD after major non-cardiac surgery (including TJR) is associated with earlier work cessation and more time on welfare (Steinmetz et al., 2009). It is conceivable that patients who undergo TJR and develop POCD are also at similar risk.

Measurement of postoperative cognitive dysfunction following total joint replacement

Many studies have investigated POCD after TJR, but have used using a variety of different methodologies. Although some studies report that TJR patients are susceptible

to POCD (Evered et al., 2011; Koch et al., 2007; Rodríguez, Torrellas, Martín, & Fernandez, 2011; Salazar et al., 2011), others report no evidence of cognitive change (Nielson et al., 1990; Patel et al., 2010; Williams-Russo et al., 1999). Consequently, it is difficult to summarise the frequency and severity of POCD after TJR from the literature in its current form. Some of the variation in these findings may be due to methodological differences between studies.

First, studies often differ with regard to what constitutes 'impairment'. For example, POCD has been variously defined as a decrease from baseline performance of two or more standard deviations on two or more cognitive measures (Salazar et al., 2011), a decrease of 20% or more on two or more cognitive measures (Koch et al., 2007), and a decrease of half a standard deviation on three or more cognitive tests (Deo et al., 2011). This variation makes it difficult to compare findings across studies because the results vary according to how conservative or lenient the definition is (Sawrie, Chelune, Naugle, & Lüders, 1996).

Studies have also differed in the measures that are used to assess POCD. Many studies have used a full neuropsychological battery, while other studies have used simple cognitive screens, such as the Mini Mental Status Examination (MMSE; Cheng et al., 2011; Duggleby & Lander, 1994; Duppils & Wikblad, 2004; Jagmin, 1998; Postler, Neidel, Günther, & Kirschner, 2011). Although screening tools are convenient and inexpensive to use, they may not be sufficiently sensitive to detect the subtle cognitive dysfunction typical of POCD (Haytmanek et al., 2010; Mitchell, 2009). This may explain the low or nonexistent rates of POCD that are reported by some of the studies that have used the MMSE (Chen et al., 2001; Haytmanek et al., 2010; Postler et al., 2011).

Studies also differ with regard to the timing of the postoperative assessment, which may occur as early as the day after surgery (Duggleby & Lander, 1994) or up to one year after surgery (Stockton, Cohen-Mansfield, & Billig, 2000). It is likely that any cognitive dysfunction detected pre-discharge - when patients are still experiencing strong pain and substantial disability, and may still be on strong pain medication - may differ to that detected at six months, when patients who have undergone TJR are likely to be nearing full physical recovery. For this reason, it is recommended that POCD assessment should occur at least three months post-surgery (Murkin, Newman, Stump, & Blumenthal, 1995). Ultimately, studies within this field differ significantly regarding the methodology used and so it is difficult gain an understanding of the incidence and severity of POCD after TJR.

Delirium

Patients who undergo TJR surgery are also susceptible to postoperative delirium; a cognitive disorder that is distinct from POCD (Krenk & Rasmussen, 2011). Delirium is defined as a disturbance in attention and awareness accompanied by cognitive deficits (e.g. problems with memory, orientation, language, or perceptual deficits) that develops abruptly and fluctuates throughout the day, and is generally transient (American Psychiatric Association, 2013). Patients with delirium will generally appear disorientated and confused, experience disruptions to their sleeping pattern and may become agitated (Krenk & Rasmussen, 2011).

There are three clinical subtypes of delirium that are recognised: hyperactive, hypoactive, and mixed (Deiner & Silverstein, 2009). Hyperactive delirium is characterised by an increase in psychomotor agitation (Alcover, Badenes, Montero, Soro, & Belda, 2013), which can present as increased hypervigilance, restlessness, and aggression, and

may be accompanied by hallucinations and delusions. Hyperactive delirium is easier to diagnose because it often leads to disorderly behaviour, such as shouting or resisting medical treatment (Martins & Fernandes, 2012; Young & Inouye, 2007). Conversely, hypoactive delirium is characterised by decreased psychomotor activity, lethargy, sleepiness and confusion. It is the more common form of delirium among older adults; however, due to its more subtle presentation, it often goes unrecognised (Young & Inouye, 2007). Lastly, the mixed delirium subtype incorporates symptoms from both the hyper and hypoactive subtypes (Inouye, 2006).

Delirium in hospitalised older adults

Delirium is extremely common among hospitalised older adults. It has been reported to occur in up to 80% of intensive care patients (Martins & Fernandes, 2012), up to 60% of post-acute care patients (Inouye, 2006) and 45% of cancer unit patients (Burns, Gallagley, & Byrne, 2004). It is also common among older surgical populations and may develop in up to 73% of those undergoing cardiac surgery (Krenk & Rasmussen, 2011), which includes rates of up to 52% following coronary artery bypass graft surgery (Alcover et al., 2013). It has also been reported to occur in 25% of patients with hip fractures (Bruce, Ritchie, Blizard, Lai, & Raven, 2007).

The specific cause(s) of delirium remain controversial (Krenk & Rasmussen, 2011); however, multiple predisposing and precipitating risk factors have been identified. Predisposing factors increase a person's vulnerability to delirium and include advanced age, a pre-existing diagnosis of dementia, sensory impairment, dehydration and malnutrition, polypharmacy, and severe comorbid medical conditions (Deiner & Silverstein, 2009; Inouye, 2006; Martins & Fernandes, 2012). Precipitating factors are acute causes that may trigger delirium, such as infection, surgery, certain medications (e.g.

benzodiazepines, narcotic analgesics and anticholinergic drugs), uncontrolled pain, lack of cognitive stimulation, lack of routine, lack of orientating information (e.g. clocks), and sleep deprivation (Inouye, 2006; Martins & Fernandes, 2012). The management and treatment of delirium often involves addressing some of these risk factors, including treating infections, dehydration and malnutrition (Inouye, 2006). Patients may also be encouraged to participate in cognitively stimulating activities, practice sleep hygiene, and use glasses and hearing aids, where appropriate, to reduce their risk of delirium (Miller, 2008).

Delirium can negatively impact on patient wellbeing in multiple ways. In the short term, it can be very stressful for both the patient and their family (Breitbart, Gibson, & Tremblay, 2002; O'Malley, Leonard, Meagher, & O'Keeffe, 2008), especially they had not been forewarned about the risk of delirium by health professionals (O'Malley et al., 2008). In the long term, delirium is associated with poorer health outcomes, even after controlling for the effects of age, comorbid medical conditions and baseline cognitive status (Bickel, Gradinger, Kochs, & Forstl, 2008; Duppils & Wikblad, 2004; McCusker, Cole, Dendukuri, Han, & Belzile, 2003). These poorer outcomes include greater functional impairment (Inouye, Rushing, Foreman, Palmer, & Pompei, 1998) and an increased risk of dementia (O'Regan, Fitzgerald, Timmons, O'Connell, & Meagher, 2013; Witlox et al., 2010), nursing home placement (Inouye et al., 1998; Siddiqi, House, & Holmes, 2006; Witlox et al., 2010) and mortality (Inouye et al., 1998; Ouimet, Kavanagh, Gottfried, & Skrobik, 2007; Siddiqi et al., 2006; Witlox et al., 2010) }. Furthermore, delirium can have significant financial implications, both for the patient and the broader health sector (Kat et al., 2008; Ouimet et al., 2007; Siddiqi et al., 2006; Witlox et al., 2010) because patients with delirium typically require longer hospital admissions (Ely et al., 2001; Ouimet et al., 2007; Siddiqi et al.,

2006; Witlox et al., 2010) and have higher health care costs (Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008).

Despite the frequency with which delirium occurs, the poor prognosis for patients and the distress it can cause, it is often misdiagnosed or goes unrecognised by health professionals (Armstrong, Cozza, & Watanabe, 1997; Davis & MacLullich, 2009; Hare, Wynaden, McGowan, Landsborough, & Speed, 2008; Inouye, Foreman, Mion, Katz, & Cooney, 2001; Rice et al., 2011). Delirium has been commonly mistaken for depression, fatigue (Armstrong et al., 1997; Spiller & Keen, 2006), schizophrenia, or dementia (Cole, 2004) due to similarities in some of the presenting symptoms. Misdiagnosis reduces the likelihood that the delirium is treated and managed appropriately (Hare et al., 2008). It is, therefore, important that health professionals, especially those who primarily work with older adults, are able to adequately diagnose, manage and treat delirium.

Delirium after total joint replacement

Patients who undergo TJR are also reported to have a significant risk of delirium (Bin Abd Razak & Yung, 2015), despite having fewer risk factors than many other patient groups (Schor et al., 1992) and better overall health than their peers (Barrett et al., 2005). Specifically, patients who undergo TJR tend to suffer few surgical complications and experience a predictable perioperative course (Talmo et al., 2010). In addition, emergency surgery is a strong risk factor for delirium (Alcover et al., 2013), but TJR is an elective procedure and candidates are required to have good pre-operative health. Indeed, surgery is often delayed or cancelled in the event of even minor pre-operative illness. Nonetheless, the majority of patients are older, TJR remains a significant and invasive operation, and patients experience significant postoperative pain that is usually treated with narcotic analgesics (Talmo et al., 2010); all of which increase the risk of

delirium (Monk & Price, 2011). Patients who develop delirium following TJR also appear to be at risk of poorer outcomes post-surgery (Bickel et al., 2008; Duppils & Wikblad, 2004), as has been reported among other patient samples (Inouye et al., 1998; Ouimet et al., 2007; Siddiqi et al., 2006; Witlox et al., 2010) }. Although limited research has examined this issue in TJR samples, the results suggest that patients who develop delirium are at risk of cognitive decline, report subjective memory impairments and need long-term care, even after controlling for age, sex, comorbid medical conditions (Bickel et al., 2008) and cognitive decline (Duppils & Wikblad, 2004). This suggests that delirium after TJR is likely to be of clinical importance.

Despite this, the frequency of delirium following TJR surgery remains unclear. Various rates have been reported, ranging from 3% (Chung, Lee, Park, & Choi, 2015) to 48% (Kinjo et al., 2012). A meta-analysis that investigated the rate of delirium among elective orthopaedic patients (which included a substantial number of, but was not limited to, TJR patients) estimated the rate of delirium to be 9% to 12% (range: 4% - 28%; (Bruce et al., 2007). However, this meta-analysis only reviewed research up to 2005. Since then, delirium has become a greater focus of TJR research and a wider range of rates have been reported, therefore it remains difficult to ascertain the true incidence of delirium following TJR.

Sources of variation in reported rates of delirium

Variation in the reported rates of delirium after TJR may be due to differences in the patient samples and methodologies used by these studies. There are many ways in which TJR samples may differ between studies, which may impact on the risk of delirium. For example, samples may differ with regard to their gender, age, and socio-economic status. Younger patients and females (Inouye, 2006), and patients with higher

socioeconomic status (Jones et al., 2010) all have a reduced risk of delirium. Samples may also differ in terms of their inclusion/exclusion criteria. For instance, some studies may recruit patients with substantial comorbidity or with preexisting cognitive impairment, whereas other studies may not recruit these patients. Patient samples may also differ with regard to surgical factors, such as the inclusion of patients who require bilateral (as opposed to unilateral) replacements, the type of anaesthesia and analgesia used, or the type of implant used. Similarly, hospital experiences may vary. For example, standard hospital procedures, such as the typical length of admission and time to mobilisation or the beginning of physiotherapy, may differ between studies. Conceivably, these differences could affect the risk of delirium after TJR.

Differences in the methodologies that are used may also affect the rates of delirium. Some studies have measured delirium retrospectively, checking medical records for notes that would suggest a patient had delirium (Shin, Kim, Ko, & Park, 2010; Wacker, Nunes, Cabrita, & Forlenza, 2006), whereas others conducted delirium assessments on a prospective basis (Bellelli, Speciale, & Trabucchi, 2005; Cerejeira, Batista, Nogueira, Vaz-Serra, & Mukaetova-Ladinska, 2013). Retrospective assessments may under-report the incidence of delirium because the treating clinician may have missed the symptoms. The measures used to assess delirium also vary ranging from delirium-specific measures - such as the Confusion Assessment Method (Kinjo et al., 2012) or the Delirium Rating Scale (Lee et al., 2011) - to broader clinical diagnostic criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders criteria; Williams-Russo, Urquhart, Sharrock, & Charlson, 1992). Other studies have assessed delirium using general cognitive screens (Sultan, 2010) or identified delirium without using a specific test or accepted criteria (Russell-Babin & Miley, 2013). These latter methods are likely to be less sensitive than delirium-specific screens (Nieuwenhuis-Mark, 2010). Finally, studies have varied with

regard to the frequency of delirium assessments and when people are assessed. As delirium fluctuates throughout the day, studies that assess for delirium more frequently and over more days postoperatively may be more likely to detect delirium (McCusker et al., 2001).

Overall, these differences in patient samples and study methodology need to be systematically summarised to determine what effect they have on reported rates of delirium and whether they account for some of the variation in the reported rates of delirium. This was investigated previously by Bruce et al. (Bruce et al., 2007), but given the increase in research on this topic, this needs to be updated.

Depression and Anxiety after Total Joint Replacement

In addition to being at risk of POCD and delirium, patients who undergo TJR are also susceptible to experiencing psychological problems, particularly depression and anxiety. These problems appear to be consistent markers for poor surgical outcomes, such as greater long-term pain and poorer physical function (Okamoto, Motomura, Murashima, & Takamoto, 2013). Therefore, a greater understanding of depression and anxiety in patients is required to support optimal recovery following TJR.

In the assessment of depression and anxiety, TJR research commonly categorises patients based on whether or not they report a clinically significant level of symptoms. These assessments often use depression and anxiety-specific scales, such as the Beck Depression Inventory (Beck, 1961) , the State-Trait Anxiety Inventory (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), or the Hospital Depression and Anxiety Scale (Zigmond & Snaith, 1983). These scales list potential symptoms or statements related to depression or anxiety, and calculate scores based on from the number and severity of

symptoms endorsed. These scores are then categorised according to whether or not they suggest a clinically significant level of depression or anxiety (Bjelland, Dahl, Haug, & Neckelmann, 2002). However, there are some drawbacks to this method of assessment. Although these scales provide a useful indicator of clinically significant distress, they do not equate to a diagnosis of depression or anxiety as defined in the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013). Furthermore, these scales rarely indicate whether patients with clinically significant distress are experiencing symptoms that align with particular types of psychological disorder (e.g. Major Depression, Adjustment Disorder, Generalised Anxiety, or a specific phobia).

Patients who undergo TJR may also be categorised according to the presence or absence of a pre-existing diagnosis of depression or anxiety. This may be determined by self-report or by checking medical records (Buller, Best, Klika, & Barsoum, 2014; Singh & Lewallen, 2013). However, this approach assumes all patients with depression and anxiety have previously sought treatment from a medical professional, which is often not the case, especially among older populations who are less likely to seek help for mental health problems (Van Zoonen et al., 2015). Therefore, this method of assessment may underestimate the rate with depression and anxiety in patients who undergo TJR.

Alternatively, the aforementioned scales may assess the extent of a patient's psychological distress by reporting number and severity symptoms they endorse. However, this method does not separate patients who experience clinically significant levels of depression and anxiety (who are likely to be of greater clinical interest) from those who experience a 'normal', or low level of depression and anxiety symptoms.

Causes of depression and anxiety in patients who undergo total joint replacement

The symptoms of depression and anxiety seen in patients who undergo surgery may be chronic or situational (reactive) in nature (Patron, Messerotti Benvenuti, & Palomba, 2014). Chronic symptoms are those that have not arisen in reaction to a stressor, but may have been present throughout a person's life and can occur throughout the population (Van Zoonen et al., 2015). Alternatively, TJR surgery may constitute a significant stressor that increases the risk of experiencing symptoms of depression and anxiety (situational/reactive). Patients who undergo TJR have suffered substantial long-term pain and disability, and the prospect of undergoing major surgery and recovery is also likely to be stressful (Gandhi, Zywiel, Mahomed, & Perruccio, 2015). When situational symptoms of depression and anxiety are sufficiently severe, they can meet the criteria of Adjustment Disorder (American Psychiatric Association, 2013), whereby symptoms develop within three months of a stressor (and should dissipate within six months once the stressor has passed); causing marked, disproportionate distress or significant impairment in important areas of function. Although the distinction between chronic and situational symptoms of depression and anxiety is rarely made within the TJR literature, it is important to consider as these symptoms are often treated differently with regard to therapy and support (Mizushima et al., 2013).

Pain is considered a significant potential trigger for depression and anxiety in patients who undergo TJR (Bonnin, Basiglini, & Archbold, 2011; Gandhi et al., 2015). Pain may be directly implicated in the development of depression (Blackburn-Munro & Blackburn-Munro, 2001) because both pain and depression occur via the nociceptive (acute response to tissue injury) and affective pathways, which correspond anatomically

(Dersh, Polatin, & Gatchel, 2002). Furthermore, both the norepinephrine and serotonin neurotransmitters are implicated, which are involved in the pathophysiology of depression and the pain-suppression mechanism (Dersh et al., 2002). Pain may also contribute to depression and anxiety via its impact on physical functioning (Duivenvoorden et al., 2013) and fatigue (Hawker et al., 2011). Pain often leads to physical disability, which may limit functional capacity in social or occupational domains, and reduce participation in pleasant or rewarding activities. Furthermore, substantial pain may cause fatigue through sleep disruption and the greater effort required to fulfill everyday tasks, which can increase the risk of depression. (Hawker et al., 2011). Pain (Bonnin et al., 2011; Lingard & Riddle, 2007; Papakostidou et al., 2012) and preoperative functional disability (Lingard & Riddle, 2007; Montin et al., 2007; Zietek et al., 2014) have consistently been reported to predict depression and anxiety in patients undergoing TJR. Therefore, depression and anxiety symptoms may, in part be due to the high levels of pain and functional disability that these patients experience.

Depression and anxiety may also result from the experience of surgery itself, which can be a significant cause of stress for patients (Pinna, Cremeans-Smith, Greene, & Delahanty, 2009). Patients who undergo TJR have been found to experience changes in their hypothalamic-pituitary-adrenal response to stress (i.e. impending surgery), which has been hypothesised to contribute to the onset of depression (Pinna et al., 2009). Patients' concerns about surgery may also cause psychological distress. Although surgery aims to relieve pain and improve quality of life, patients who undergo elective surgery know they will need to endure greater pain and disability in the early postoperative stages (Jawaid, Mushtaq, Mukhtar, & Khan, 2007) and that good recovery is not guaranteed (Jawaid et al., 2007; Pinna et al., 2009). Patients may also worry about the risks of surgical complications (Jawaid et al., 2007). Other causes of stress associated with TJR may

include a lack of autonomy, being in a hospital environment, and isolation (Smolderen, 2010). Ultimately, there are multiple ways that TJR surgery may cause stress, which can then lead to symptoms of depression and anxiety.

Depression, anxiety, and postoperative outcomes

The symptoms of depression and anxiety are unpleasant experiences in themselves and they may also place patients who undergo TJR at a greater risk of negative post-surgical outcomes, whether experienced pre- and/or postoperatively. Pre-operative depression and anxiety are also associated with greater pain (Blackburn, Qureshi, Amirfeyz, & Bannister, 2011; Brander, Gondek, Martin, & Stulberg, 2007; Duivenvoorden et al., 2013; Judge et al., 2012) and poorer function up to one year post-surgery (Brander et al., 2007; Duivenvoorden et al., 2013). In addition, pre-operative depression can also predict activity limitation and dependence on walking aids for up to five years after surgery (Singh & Lewallen, 2010). Reductions in depression and anxiety after TJR have been found to be associated with improvements in physical function (Blackburn et al., 2011; Swinkels & Allain, 2013)}. Therefore, pre-operative symptoms of depression and anxiety may increase the risk of negative post-surgical outcomes, while a reduction in symptoms may further improve post-surgical outcomes

It is also possible that the symptoms of depression and anxiety have a direct effect post-surgical pain and function (Carney, Freedland, Miller, & Jaffe, 2002). Patients with depression may be less likely to fully engage in rehabilitation (Carney et al., 2002), be less adherent to medical treatment (DiMatteo, Lepper, & Croghan, 2000), less physically active during their recovery, and perceive themselves as less physically adept (Brander et al., 2007; Pomp, Fleig, Schwarzer, & Lippke, 2012). In addition, the symptoms of anxiety may increase the risk of poor outcomes through avoidance behaviours that limit recovery and

heighten pain sensitivity (Dersh et al., 2002). Alternatively, it is also possible that the symptoms of depression and anxiety do not cause poor outcomes, but are merely correlated (Carney et al., 2002). For example, people with depression have a greater risk of other illnesses - such as hypertension, diabetes and heart disease (Wells, Golding, & Burnam, 1989) - all of which may explain the higher levels of pain and poorer functional recovery after TJR (Amusat et al., 2014; Elmallah, Cherian, Robinson, Harwin, & Mont, 2015; Fisher, Dierckman, Watts, & Davis, 2007; Singh & Lewallen, 2013). Ultimately, the nature of the relationship between depression/anxiety and surgical outcomes is not clear; however, as depression and anxiety are a consistent marker for poor outcomes, this warrants further attention.

The impact of total joint replacement surgery on depression and anxiety

Patients who undergo TJR appear to experience higher rates of clinically significant depression and anxiety compared to the general population. Pre-operative rates of depression reportedly range from 20% to 35% (Duivenvoorden et al., 2013; Riddle, Wade, & Jiranek, 2010; Riediger, Doering, & Krismer, 2010; Utrillas-Compaired, De la Torre-Escuredo, Tebar-Martinez, & Asunsolo-Del Barco, 2014), whereas rates of anxiety range from 16% to 57% (Duivenvoorden et al., 2013; Nickinson, Board, & Kay, 2009; Riddle et al., 2010; Utrillas-Compaired et al., 2014). Up to 50% of patients suffer from depression and 44% experience anxiety prior to hospital discharge (Nickinson et al., 2009). By six to twelve months post-surgery, patients should be near full surgical recovery; however 10% to 28% still experience clinically significant depression and 11% to 30% experience anxiety (Duivenvoorden et al., 2013; Utrillas-Compaired et al., 2014). As

a comparison, the rates of depression and anxiety for the general population are estimated to be 4% and 9.8%, respectively (Australian Bureau of Statistics, 2009).

It also unclear what effect TJR has on the number of depression and anxiety symptoms that patients may experience. The mean number of symptoms pre- to post-surgery has been reported to increase (Faller, Kirschner, & König, 2003; Nickinson et al., 2009), remain constant (Attal et al., 2014; Montin et al., 2007; Salazar et al., 2011) and decrease (Duivenvoorden et al., 2013; Stecz & Kocur, 2014; Utrillas-Compaired et al., 2014). Therefore, it is yet to be determined whether TJR surgery has an effect, positive or negative, on symptoms of depression and anxiety.

Overall, it is not clear to what degree patients who undergo TJR experience clinically significant levels of psychological distress before and after surgery. This is of clinical importance as psychological problems are considered to have negative impacts on patient recovery. While much of the literature suggests that patients are at an increased risk of depression and anxiety compared to the general population, this should be confirmed through a comprehensive and systematic analysis of the literature.

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Chapter 2. Postoperative Cognitive Dysfunction and Cognitive Reserve.

Multiple factors have been suggested as potential causes of POCD after TJR, including the type of anaesthesia used during surgery and the analgesia required after surgery, but research has not supported these explanations (Fong, Sands, & Leung, 2006; Guay, 2011). Cerebral microemboli, which are small particles that are released into the bloodstream and travel to the brain during surgery, have also been investigated as a potential cause of POCD (Koessler & Pitto, 2002). However, the few studies that have investigated the association between cerebral microemboli and POCD following TJR surgery have not supported a relationship (Gray, Torrens, Howie, Christie, & Robinson, 2008; Koch et al., 2007; Rodriguez et al., 2005).

Although this challenges the notion that cerebral microemboli causes POCD, it is also possible that the relationship is moderated by another variable. Moderation occurs when the strength or direction of a relationship between two variables is affected by the presence of a third factor (Baron & Kenny, 1986). Cognitive reserve is one variable that may moderate the relationship between microemboli and POCD (Kneebone, Luszcz, Baker, & Knight, 2005). Reserve has been used to explain the failure to find a consistent relationship between the amount of brain pathology and the associated clinical symptoms (Stern, 2002). Hence, two people may experience identical brain injuries/pathology, but one may suffer significantly greater incapacity than the other (Barnett, Salmond, Jones, & Sahakian, 2006; Jones et al., 2010; Satz, Cole, Hardy, & Rassovsky, 2011). In theory, patients who undergo TJR surgery and that experience a significant load of intraoperative cerebral microemboli, but have high levels of reserve, may experience few (if any) symptoms of POCD; whereas patients with low reserve may experience significant dysfunction. If reserve moderates the relationship between microemboli and POCD, it is

unlikely that there would be a direct linear relationship between the two. It should be initially established whether cognitive reserve can predict the development of POCD, to determine whether future research should be examine cognitive reserve as a potential moderator.

Brain and Cognitive Reserve

There are multiple terms and definitions for reserve; the most common being 'brain reserve' and 'cognitive reserve' (Depp, Harmell, & Vahia, 2012; Robertson, 2014; Stern, 2009). Brain reserve refers to the protection against cognitive dysfunction that is afforded by brain structure and is typically measured using physical indicators, such as brain volume, head circumference, or synaptic count (Staff, 2012; Stern, 2009). Brain reserve is thought to represent a 'threshold model' of reserve. When brain damage occurs, a person will be protected from cognitive impairment until a certain level of damage is reached. Once that level of damage is surpassed, cognitive decline occurs. (Barulli & Stern, 2014; Satz et al., 2011). People with higher levels of brain reserve are thought to have a higher threshold for damage and can therefore withstand greater brain injury before experiencing any dysfunction. For this reason, brain reserve is also described as a 'passive' conceptualisation of reserve, because cognitive dysfunction is thought to be inevitable once a certain degree of injury is sustained (Stern, 2009).

Cognitive reserve, on the other hand, is conseptualised as an 'active' form of reserve, because it enables the brain to actively cope with brain injury using cognitive and compensatory strategies (Stern, 2009). Specifically, cognitive reserve refers to individual differences in processing efficiency and the capacity to compensate for impairment through adaptations within the neuronal networks (Staff, 2012; Stern, 2009; Watson &

Joyce, 2015). This view of reserve does not presume that a threshold of damage exists (beyond which cognitive decline is assured); rather it posits that individual differences in brain processes can provide additional protection against cognitive decline (Stern, 2009). Cognitive reserve is typically assessed using indirect or proxy measures of cognitive capacity, including educational or occupational attainment, literacy, IQ, and the pursuit of cognitively stimulating leisure activities (Staff, 2012; Stern, 2009).

Stern (Stern, 2002, 2009) proposed that cognitive reserve may be divided into two components: neural reserve and neural compensation. Neural reserve refers to differences in the efficiency, capacity and flexibility of the cognitive processes that are required to perform a task. People with more efficient and flexible processes are thought to be better at coping with any disruption to cognition that is caused by brain injury. Neural compensation refers to differences in the ability of the brain to cope with damaged processing networks by adopting other neural networks that would not typically be used for these functions. Greater neural reserve and neural compensatory abilities are thought to be protective in the event of brain injury (Stern, 2002, 2009).

Throughout the literature, brain reserve generally refers to brain physicality (Jones et al., 2010) and cognitive reserve refers to how the brain is used (Stern, 2009). However, the two concepts inevitably overlap (Staff, 2012; Watson & Joyce, 2015) because both are likely to be shaped by genetics and the environment. For example, individuals who are genetically equipped with more neurons and a larger brain may show more intellectual promise at an early age, receive higher quality education and achieve greater occupational attainment (Staff, 2012). Furthermore, cognitive training has been associated with structural changes to the brain (Barulli & Stern, 2014). Although this thesis focuses on, and refers to cognitive reserve only; it is not assumed that cognitive reserve is an entirely separate concept to brain reserve.

The Relationship between Cognitive Reserve and Cognitive Decline.

Cognitive reserve has proven to be a consistent predictor of cognitive dysfunction. Specifically, it has been reported to be protective against dementia in the general population (Hall et al., 2009; Prince et al., 2012) and against age-related cognitive decline in healthy older adults (James, Wilson, Barnes, & Bennett, 2011). Cognitive reserve also reportedly predicts the rate and severity of decline in samples with neurodegenerative disorders, including Alzheimer's disease (Osone, Arai, Hakamada, & Shimoda, 2014), vascular dementia (Lane, Paul, Moser, Fletcher, & Cohen, 2011), multiple sclerosis (Booth et al., 2013; Scarpazza et al., 2013), Huntington's disease (Bonner-Jackson et al., 2013) and Parkinson's disease (Sánchez, Rodríguez, & Carro, 2002). In addition, cognitive reserve is related to cognitive decline in patients with non-neurological diagnoses, such as heart failure (Miller et al., 2012) and depression (Murphy & O'Leary, 2010).

Research has also examined whether cognitive reserve may act as a moderator between brain pathology and cognitive decline. For example, cognitive reserve has been found to moderate the relationship between subcortical hyperintensities and cognition in patients with vascular dementia (Lane et al., 2011). Furthermore, cognitive reserve appears to moderate the relationship between cortical atrophy and cognitive decline in patients with multiple sclerosis (Booth et al., 2013).

It is therefore conceivable that cognitive reserve may play a role in the development of POCD after TJR (Kneebone et al., 2005), potentially moderating the relationship between cerebral microemboli (or other causes of cognitive dysfunction) and POCD. Specifically, embolic load may trigger measurable POCD among patients with low

cognitive reserve, while patients with high cognitive reserve may not develop any/many symptoms. This may explain why research has failed to find a direct relationship between microemboli and POCD after TJR.

Cognitive Reserve and Postoperative Cognitive Dysfunction after Total Joint Replacement

To date, there are very few studies that have examined the link between cognitive reserve and POCD following elective surgery, and none have specifically examined this is TJR samples. Given the divergent findings in previous studies regarding the incidence of POCD following TJR, it was thought important to consider whether cognitive reserve may influence the development of POCD. In addition, the assessment of cognitive reserve among a TJR sample provides a unique opportunity to add to the field of cognitive reserve research. Finally, if cognitive reserve is found to predict POCD outcomes following TJR, it may provide opportunities for future therapeutic interventions.

Methodological limitations in many previous studies have presented a significant obstacle in clarifying the relationship between cognitive reserve and cognitive dysfunction.. Cognitive change has been assessed in healthy older adults in addition to many different clinical samples, and has adopted either a longitudinal or cross-sectional approach. In longitudinal research, participants undergo repeat assessments over time and cognitive performance is compared to the baseline assessment. Although these studies allow for the assessment of change over time, they are vulnerable to repeat testing confounds (e.g. practice effects, regression to the mean, measurement error). Unfortunately, very few longitudinal studies that have examined reserve have additionally used a control group, which makes it difficult to disentangle genuine cognitive change from the effects of these

confounds. Despite this limitation, longitudinal studies have provided at least partial support for the protective role of cognitive reserve against cognitive decline in multiple patient groups (Benedict, Morrow, Weinstock Guttman, Cookfair, & Schretlen, 2010; Bonner-Jackson et al., 2013; Hall et al., 2009; James et al., 2011; Liu et al., 2012; Prince et al., 2012; Sattler, Toro, Schönknecht, & Schröder, 2012).

More frequently, cross sectional designs have been used within research that has examined reserve. Although these studies cannot measure change over time, they frequently include a control group, for comparison. Cross-sectional support for the protective role of cognitive reserve has been extensively reported in many different patient groups (Barulli, Rakitin, Lemaire, & Stern, 2013; Booth et al., 2013; Feinstein, Lapshin, O'Connor, & Lanctôt, 2013; Fyffe et al., 2011; Ghaffar, Fiati, & Feinstein, 2012; Lane et al., 2011; Osone et al., 2014; Sánchez et al., 2002; Sánchez, Torrellas, Martín, & Barrera, 2011; Scarpazza et al., 2013; Spitznagel & Tremont, 2005).

The use of a TJR sample and a controlled, longitudinal research design to examine the relationship between cognitive reserve and POCD provides a unique opportunity to add to the reserve literature. By using elective surgery patients, a pre-surgical assessment can be conducted, which is generally not possible with other forms of brain injury (e.g. cognitive dysfunction that may develop after emergency surgery, stroke, or traumatic brain injury). To our knowledge, only one study has examined the impact of reserve on POCD after elective surgery, specifically elective coronary artery bypass graft surgery (Ropacki, Bert, Ropacki, Rogers, & Stern, 2007). These patients have also been reported to develop POCD (Evered, Scott, Silbert, & Maruff, 2011; Pugsley et al., 1994; Ropacki et al., 2007; Selnes & Gottesman, 2009) and this is thought to be caused, in part, by intraoperative cerebral microemboli (Stump, Rogers, Hammon, & Newman, 1996). Furthermore, it has been argued that patients who undergo coronary artery bypass graft

surgery receive a relatively consistent type of brain injury (Kneebone, 2002), as might TJR patients, adding another form of control to the study design. Ultimately, Ropacki et al. found that cognitive reserve did not predict POCD; however, this finding may partly be attributable to a number of methodological issues. First, this study did not use a control group, therefore it was not possible determine whether repeated testing impacted on the findings. Second, cognitive reserve (estimated premorbid IQ) was dichotomised as low/high instead of being treated as a continuous variable, which reduces statistical power.(Altman & Royston, 2006) In addition, no other measures of cognitive reserve were used (e.g. education, occupational attainment, engagement in cognitively stimulating leisure activities). Finally, patients were assessed for cognitive problems prior to hospital discharge (within one week of surgery), which may be too soon because cognitive function can be unstable at this time (Murkin, Newman, Stump, & Blumenthal, 1995). Overall, although the study by Ropacki et al. is distinctive within the field of cognitive reserve research, the design used may be improved upon through the use of a control group, a sensitive and comprehensive measure of cognitive reserve, and a longer follow-up interval. This can be achieved using sample of patients undergoing TJR.

Investigating the relationship between cognitive reserve and POCD may also have implications for clinical practice and future research. If cognitive reserve is found to predict POCD, then future research on the causes of POCD should also examine cognitive reserve as a potential moderator. This has not been done in existing research, which may explain the lack of significant findings between the potential causes of cognitive dysfunction (e.g. cerebral microemboli) and the development of POCD (Gray et al., 2008; Koch et al., 2007; Rodriguez et al., 2005). This may help clarify the cause(s) of POCD, which may then be targeted by intervention studies to reduce the risk of POCD.

In addition, cognitive reserve itself may be investigated as a potential target for intervention. If greater levels of cognitive reserve protect against cognitive dysfunction, then this would warrant an investigation into strategies to increase cognitive reserve prior to elective surgery in order to reduce the risk of POCD. Although cognitive reserve is generally considered to be a protective mechanisms against dysfunction that is built up over a person's lifetime (e.g. through education, occupational attainment), it is thought that cognitively stimulating activity in late life may also contribute to greater levels of cognitive reserve (Stern, 2012), and a reduction may be detrimental. For example, a decrease in cognitively stimulating activities upon diagnosis of multiple sclerosis is associated with greater cognitive decline, even after controlling for premorbid IQ, demographics and degree of disability (Booth et al., 2013). It has been suggested that interventions to increase cognitive reserve in late life may also help to increase reserve and slow cognitive decline in patients with Alzheimer's disease (Stern, 2012). However, it remains unclear whether short-term interventions to improve reserve would be sufficient to have an impact on actual cognitive decline (Barulli & Stern, 2014). If cognitive reserve does predict POCD after TJR, short-term interventions to increase cognitive reserve may be feasible. Such interventions could take place over 6 to12 months, while patients are waitlisted for TJR surgery. However, it should first be determined whether cognitive reserve helps to predict POCD after TJR.

Overview, Aims and Thesis Structure

Total joint replacement (TJR) of the hip or knee is a common procedure among the older adult population (Australian Orthopaedic Association National Joint Replacement Registry, 2015) and the demand for this surgery is increasing (Australian Orthopaedic

Association National Joint Replacement Registry, 2016a, 2016b). It is often used as a treatment for end-stage osteoarthritis, which can cause substantial pain and functional disability (Arya & Jain, 2013). Research has supported the positive impact of TJR on patient health and quality of life (Talmo, Robbins, & Bono, 2010); however, there is less clarity with regard to the effect of TJR on non-surgical outcomes, specifically POCD, delirium, depression and anxiety.

POCD is increasingly recognised as a problem following TJR surgery (Koch et al., 2007; Salazar et al., 2011) and is associated with poorer health and quality of life outcomes, such as reduced functional capacity and earlier work cessation (Moller, Cluitmans, & Rasmussen, 1998; Newman et al., 2001; Phillips-Bute et al., 2006; Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009). Despite the clinical importance of POCD, the existing literature has provided mixed findings regarding the magnitude of this problem in TJR samples (Gray et al., 2008; Koch et al., 2007; Patel, Stygall, Harrington, Newman, & Haddad, 2010). Therefore, the first aim of this thesis was to systematically review and evaluate the literature on POCD in TJR in order to clarify the incidence (i.e. the proportion of patients who develop POCD following TJR surgery) and severity of POCD after TJR (Study 1; Chapter 3). POCD was examined in terms of different cognitive domains (e.g. memory, attention, executive function) and according to the assessment interval (pre-discharge, 3-6 months post-surgery).

In addition to POCD, delirium has been identified as a potential complication of TJR. Delirium is associated with poorer post-surgical outcomes, including cognitive decline and nursing home placement (Bickel, Gradinger, Kochs, & Forstl, 2008; Duppils & Wikblad, 2004). However, the reported rates of delirium vary substantially, meaning the extent to which delirium is a problem following TJR surgery is unclear. This variation may partly be attributable to differences in the samples that are examined (e.g. whether TJR

samples included or excluded patients with pre-existing cognitive impairment), the TJR procedure itself (e.g. type of anaesthesia), and how delirium is assessed (e.g. frequency of assessment, measure used). Therefore, the second aim of this thesis was to evaluate the literature on delirium after TJR in order to determine the incidence (i.e. the rate of patients who develop delirium during hospital admission) and whether reported rates varied according to sample or methodological differences between studies. To this end, Chapter 4 (Study 2) details a meta-analysis that examined the incidence of delirium following TJR, and the impact of differences in patient samples, the procedure, and delirium assessment on these rates.

Patients who undergo TJR are also susceptible to a number of psychological problems, such as depression and anxiety (Duivenvoorden et al., 2013; McHugh, Campbell, & Luker, 2013). This may result from chronic pain, disability, and the stress of undergoing a major surgical procedure. Depression and anxiety are thought to negatively affect patient health, both directly and indirectly, which may contribute to poorer post-surgical pain and physical function (Gandhi, Zywiel, Mahomed, & Perruccio, 2015; Hawker et al., 2011; Pinna, Cremeans-Smith, Greene, & Delahanty, 2009). Existing research has yielded mixed findings regarding the rate of clinically significant levels of depression and anxiety pre- and post-TJR surgery, and the effect that TJR surgery has on these symptoms. It is of clinical importance to determine how frequently patients who undergo TJR experience these problems, and the likely course of these symptoms before and after surgery. Therefore, the third aim of this thesis was to evaluate the literature to determine the prevalence (i.e. the proportion of patients that have clinically significant levels of depression and anxiety at a specific point in time) and severity of clinically significant levels of depression and anxiety pre- and post-surgery, and to examine whether these symptoms increase, remain constant, or decrease in the short- and longer-term following

surgery (Study 3; Chapter 5). Depression and anxiety were examined pre-surgery and up to one year post-surgery, and both the prevalence and number of symptoms were considered.

The fourth aim of this thesis was to conduct a clinical study to address any gaps in the POCD literature that were identified by the preceding studies, particularly Study 1. To this end, Chapter 6 outlines a clinical study that assessed the incidence and severity of POCD in patients who underwent TJR using a pre- post-surgery independent-groups design (TJR patients, Healthy Controls). All participants were assessed using multiple cognitive tests and quality of life measures. Demographic, medical, and surgical details (TJR patients only) were also collected. Patients undergoing TJR were assessed in the three weeks prior to surgery and six months after surgery. Healthy controls were assessed over an equivalent interval. Given the focus on POCD, it was of interest to then investigate whether cognitive reserve may influence the recovery of TJR patients. The protective role of cognitive reserve against cognitive decline has been investigated in multiple patient groups (Booth et al., 2013; Lane et al., 2011), but does not appear to have been examined in the context of POCD following TJR. Therefore, the final aim of this thesis was to determine whether cognitive reserve could predict the development of POCD after TJR.

In summary, the principal objectives of this thesis were to:

1. Meta-analyse the literature that has examined cognitive and psychological outcomes after TJR in order to determine, a) the incidence and severity of POCD; b) the incidence of delirium and the impact of different sample characteristics and measures of delirium on incidence rates; and c) the

prevalence of clinically significant levels of depression and anxiety and the change in symptoms severity pre- to post-surgery.

2. Conduct a clinical study to assess the incidence and severity of POCD following TJR and to address some of the methodological limitations observed in previous research on this topic.
3. Examine whether cognitive reserve is related to the development of POCD in patients who undergo TJR.

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Chapter 3. Study 1

Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: A meta-analysis

This chapter presents a published paper, the details of which are:

> Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2014). Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: A meta-analysis. *Journal of Arthroplasty, 29,* 261-267. doi:10.1016/j.arth.2013.06.007.

In the published paper, 'Total Joint Replacement' is referred to as 'Total Joint Arthroplasty as per the Journal's requirements. To maintain consistency the term total joint replacement has been retained here with the exception of the study title.

Statement of Authorship

Statement of Authorship

Title of Paper	Postoperative cognitive dysfunction after total joint arthroplasty in the elderly: A meta-analysis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
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Contribution to the Paper	Conducted literature searches, coded articles, analysed and interpreted data, wrote manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Preface

Chapter 1 reviewed the research evidence for POCD after TJR, and reported mixed findings, making it difficult to reach any firm conclusions on this topic. It was posited that differences in research methodology may account for some of the variation in study results.

This chapter presents a meta-analysis that systematically evaluated the literature on POCD after TJR. Data from individual studies were examined in terms of the type of data that were reported, the length of time between surgery and the follow-up assessment, and the cognitive measures that were used to assess cognitive dysfunction. The primary aim was to determine the incidence and severity of POCD after TJR

Abstract

This meta-analysis consolidated the research on postoperative cognitive dysfunction (POCD) following total joint replacement (TJR). Data from 17 studies that assessed cognition pre- and post-surgery in TJR patients alone (15 studies) or matched TJR and control groups (2 studies) were analysed. Results were grouped by cognitive domain (memory, attention, language, speed, general cognition) and follow-up interval (pre-discharge, 3-6 months post-surgery). The TJR data revealed small declines in reaction time and general cognition pre-discharge, but no evidence of decline 3-6 months post-surgery. Very limited TJR and Control data indicated no group differences in the changes to performance over time; however, the TJR group was cognitively compromised pre- and post-surgery compared to Controls. Further appropriately controlled research is required to clarify whether POCD commonly occurs after TJR.

Total joint replacements of the hip and knee (TJR) are among the most common major surgeries performed on older adults (Harris & Sledge, 1990). The number of TJRs performed each year has increased substantially over the last decade (Australian Orthopaedic Association National Joint Replacement Registry, 2012) and this trend is predicted to continue as our population ages. TJRs are usually performed to treat damage caused by osteoarthritis (Australian Orthopaedic Association National Joint Replacement Registry, 2012), which is common among older adults, and typically yield good surgical outcomes as they markedly improve pain, physical function, and have few medical complications (Labek, Thaler, Janda, Agreiter, & Stockl, 2011). Although surgically successful, patients may still experience short- or long-term postoperative cognitive dysfunction (POCD; Ancelin et al., 2010; Evered, Scott, Silbert, & Maruff, 2011; Williams-Russo et al., 1999), which is a subtle form of cognitive decline that can develop after surgery and affect multiple cognitive domains, particularly in the elderly (Deiner & Silverstein, 2009).

There are multiple theories regarding the cause of POCD. One is that it results from intra-operative microemboli that travel to the brain. These emboli are thought to be released when the artificial prosthesis is inserted or the tourniquet that is used during surgery is removed (Koessler & Pitto, 2002). Other potential causes of POCD include general anaesthesia and/or postoperative analgesia (Fong, Sands, & Leung, 2006); although research has consistently failed to find a relationship between general anaesthesia and POCD after TJR (Evered, Scott, et al., 2011; Jones et al., 1990; Nielson et al., 1990). Furthermore, a systematic review that investigated the potential role of analgesia in postoperative cognitive problems confirmed that POCD was not related to

either the type of analgesia or its method of administration (Fong et al., 2006). Thus, the underlying cause of POCD has yet to be established.

The actual incidence of POCD after TJR is presently unclear, with some studies reporting substantial rates (Ancelin et al., 2010; Deo, West, Butcher, & Lewis, 2011; Evered, Scott, et al., 2011; Koch et al., 2007; Salazar et al., 2011) and others failing to find evidence of cognitive dysfunction (Jones et al., 1990; Patel, Stygall, Harrington, Newman, & Haddad, 2010). Moreover, the incidence rates reported by those studies that did find evidence of POCD following TJR are highly variable, ranging from 16% to 45% (Evered, Scott, et al., 2011; Koch et al., 2007), with both rapid recovery (Duggleby & Lander, 1994) and chronic dysfunction (Ancelin et al., 2010) also noted.

Some of the variability in these research findings may result from between-study methodological differences. For example, the existing POCD studies differ in terms of their mean age, sample sizes, sample composition (i.e. TJR patients only versus partial/revision procedures plus TJR), research design (i.e. TJR group only versus TJR and Control groups), follow-up interval, and the definition of clinically significant change (i.e. use of reliable change indices versus cut-off scores). There are also differences in how cognition is measured, as both detailed cognitive batteries (Ancelin et al., 2010; Evered, Scott, et al., 2011; Salazar et al., 2011) and basic screening tools, such as the Mini Mental Status Examination (MMSE; McCaffrey, 2009; Postler, Neidel, Günther, & Kirschner, 2011), have been used. Moreover, differences in the ability of individual tests to detect subtle cognitive dysfunction may impact on the reported incidence, severity, and duration of POCD.

Importantly, research suggests that POCD may negatively impact on the post-surgical quality of life of patients and their families. While this area remains under-

researched in TJR patients, there is comparable evidence in cardiac and general hospital inpatients suggesting that POCD is associated with enduring negative effects, even after controlling for potential confounding factors, such as age and comorbid medical conditions (M. F. Newman et al., 2001; Phillips-Bute et al., 2006). For example, cardiac patients who developed cognitive problems within six weeks of their surgery also experienced a range of other problems one year later (Phillips-Bute et al., 2006). Specifically, they had reduced functional capacity, were more limited by their symptoms (e.g. shortness of breath interfered more with their daily activities), and reported more cognitive difficulties (Phillips-Bute et al., 2006). Based on research conducted with general surgery patients, POCD may also have significant financial implications for both TJR patients and the wider community (Moller, Cluitmans, & Rasmussen, 1998; Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009). For instance, patients who developed POCD are reportedly more likely to leave the labor market prematurely and to spend more time on welfare (Steinmetz et al., 2009), and require more assistance with their activities of daily living (Moller et al., 1998). While research of this type has yet to be conducted with TJR patients, it might be expected that TJR patients with POCD would be similarly affected.

Despite the high incidence of TJR in the older population and the potential burden associated with the development of POCD, the nature and extent of POCD after TJR remains poorly understood. There is little consistency in the research findings, and the literature specifically relating to POCD after TJR has not been reviewed, either qualitatively or quantitatively. Rather, current reviews of post-surgical cognitive outcomes have either focused on cardiac surgery (Cormack et al., 2012; Dunkel et al., 2009) or have combined data from patients that have undergone different forms of surgery (Guay, 2011; S. Newman, Stygall, Hirani, Shaefi, & Maze, 2007). The absence of an over-arching analysis of existing research on POCD following TJR represents a major obstacle to our

understanding of the incidence and severity of these problems. The current meta-analysis synthesised the available research data in order to provide this information.

Methods

Search strategy and selection criteria.

Comprehensive searches of the PubMed, PsycINFO, Embase and Scopus electronic databases were undertaken to locate all studies that assessed cognition among older adults after TJR that were published between January 1980 and August 2012. A complete list of the search terms is provided in Appendix A.

To be eligible for inclusion, studies had to have: (1) included a surgical group who underwent TJR of the hip or knee; (2) examined participants who were over 50 years of age (or mean age minus 1 SD ≥ 50 years); (3) assessed cognition using standardised neuropsychological tests (excludes self-report measures and clinician ratings); (4) performed pre- and post-surgical cognitive assessments of either one (TJR) or two (TJR, Control) samples; (5) completed at least one post-surgical assessment 24 hours or more after surgery; (6) provided data that would allow for the computation of an effect size (e.g. proportions, means and SDs, or exact t-values); (7) assessed participants who were not reported to have had a neurological (e.g. dementia) or medical condition that may have impacted on cognition; (8) a sample size that was greater than one (excludes case studies); and (9) been published in a journal in English.

Studies were deemed eligible for inclusion if they included patients who had 'elective' hip and knee surgery. Although this term can be used to refer to partial and revision procedures (in addition to TJR), these procedures usually only constitute a small number of elective surgery patients (Australian Orthopaedic Association National Joint

Replacement Registry, 2012). Therefore, where TJR data were not reported separately, studies that assessed samples of elective surgery patients were assumed to consist primarily of TJR patients.

If a study that was published within the previous decade did not provide the necessary data, but was otherwise eligible, the corresponding author was contacted by email to request these data. The authors of eleven studies were contacted for this purpose (Ancelin et al., 2010; Bickel, Gradinger, Kochs, & Forstl, 2008; Deo et al., 2011; Evered, Scott, et al., 2011; Gray, Torrens, Howie, Christie, & Robinson, 2008; Koch et al., 2007; Kudoh, Takase, & Takazawa, 2004; Li, Xi, An, Dong, & Zhou, 2012; Lowery, Wesnes, Brewster, & Ballard, 2008; Salazar et al., 2011)[4, 5, 12-14, 27-31], five of whom provided the requisite data (Deo et al., 2011; Gray et al., 2008; Koch et al., 2007; Lowery et al., 2008; Salazar et al., 2011).

The original literature search was kept broad in order to capture the maximum number of potentially relevant papers and identified 1,312 studies (excluding duplicates). An examination of the titles and abstracts of these papers revealed that approximately 65% were not relevant to either TJR or POCD. A further 25% were relevant to TJR only, while approximately 5% addressed POCD, but not in a TJR sample. The full-texts of the remaining 5% were screened using the inclusion criteria to determine their eligibility, with 19 studies being eligible for inclusion. The most common reasons for the exclusion of studies were a failure either to provide the data for TJR patients separately from that of other surgical patients or to conduct a post-surgical cognitive assessment (i.e. only pre-surgical assessments completed). Meta-analyses assume that the data from different studies are independent and, therefore, that each sample only contributes once to the calculation of a mean effect-size (Lipsey & Wilson, 2001). If sample independence could not be established through the information provided in the publication, the corresponding

authors were contacted by email for confirmation. When samples overlapped, the respective studies were combined and treated as one. To this end, the data from two studies by Evered et al (2011; 2011) were combined, as were the data from two studies by Dupplis and Wikblad (2000, 2004). Therefore, the data from a total of 17 independent studies were analysed in this study.

Research design and data preparation

Four of the 17 studies used an experimental design to examine whether different types of anaesthesia resulted in different cognitive outcomes following TJR (Cheng et al., 2011; Jones et al., 1990; Nielson et al., 1990; Williams-Russo et al., 1999). Only the 'standard care' patients (the control group) from Cheng et al. (2011) could be included in the current meta-analysis, as the experimental group received non-standard treatment. In contrast, both the experimental and surgical control groups from Jones et al. (1990), Nielson et al. (1990) and Williams-Russo et al. (1999) received standard care TJR; consequently these groups were combined for current purposes, and means and SDs for the total TJR sample calculated. In addition, two studies provided mean (and SDs) cognitive scores for specific subgroups; namely the presence/absence of POCD (Rodriguez et al., 2005) or post-surgical delirium (Lowery et al., 2008). As these subgroups were not required for the current meta-analysis, their data were combined to provide an overall mean and SD for the entire sample. Thus, the data that was extracted from these six studies equated to that of a single-sample pre- and post-surgery design, and hereafter will be referred to as such.

Of the 17 studies that assessed cognition after TJR, 15 used a single-sample pre- and post-surgery design (Cheng et al., 2011; Deo et al., 2011; Duggleby & Lander, 1994; Duppils & Wikblad, 2004; Gray et al., 2008; Jones et al., 1990; Koch et al., 2007; Lowery

et al., 2008; McCaffrey, 2009; Nielson et al., 1990; Patel et al., 2010; Postler et al., 2011; Rodriguez et al., 2005; Stockton, Cohen-Mansfield, & Billig, 2000; Williams-Russo et al., 1999) and only two used a two-sample (TJR and Controls) pre- and post-surgery design (Evered, Scott, et al., 2011; Salazar et al., 2011). Given that very few studies used the latter design, the TJR data from these two studies were additionally treated as if they came from a single-sample pre- and post-surgery design (i.e. TJR data analysed, control group data excluded) and tabled with the other studies that used this design for comparative purposes.

Cognition was assessed using a wide variety of different tests, and many studies used either the same test or a close variant (e.g. Grooved Pegboard Task and the Purdue Pegboard Task). When tests were deemed to measure the same construct, they were analysed together and given a more generic label (e.g. motor speed). For reporting purposes, all tests were grouped into five broad cognitive domains, based on those identified by Lezak et al. (2012): memory, attention, language, motor and processing speed, and general cognition.

Studies also varied considerably with regard to the interval that elapsed between the TJR surgery and the follow-up cognitive assessment; ranging from one day to 12 months. For current purposes, all assessments were combined into one of two follow-up intervals: pre-discharge (within one week of surgery) and longer follow-up (3 to 6 months post-surgery). With two exceptions, these groupings captured all of the available data, with only the six-week follow-up from Patel et al. (2010), and one-year follow-up from Stockton et al. (2000) being excluded. Both of these studies conducted two cognitive assessments that fell within the longer follow-up interval that was used here (3-6 months post-surgery), but each study can only contribute one effect to the calculation of a mean. Therefore, only the three-month data from Patel et al. (2010) and the 6-month follow-up

data from Stockton et al. (2000) were used, as these assessments were more comparable to the follow-up intervals of the other studies.

. Surgical procedures can vary in terms of the type of implant that is used (i.e. cemented or uncemented/press-fixed) and whether or not a tourniquet is used in total knee replacements, which may contribute to surgical outcomes. Information relating to these two variables was obtained from each study. Unfortunately, nine studies did not report this information (Chen et al., 2001; Duggleby & Lander, 1994; Duppils & Wikblad, 2004; Evered, Scott, et al., 2011; Jones et al., 1990; Lowery et al., 2008; McCaffrey, 2009; Nielson et al., 1990; Stockton et al., 2000), three used a combination of methods but did not provide separate data for each (Koch et al., 2007; Patel et al., 2010; Postler et al., 2011), and the remaining five studies reported using only one of these subgroups (cemented implants; Deo et al., 2011; Gray et al., 2008; Rodriguez et al., 2005; Williams-Russo et al., 1999), (tourniquets; Deo et al., 2011; Rodriguez et al., 2005; Salazar et al., 2011; Williams-Russo et al., 1999). Therefore, it was not possible to examine the impact of these two variables on cognitive outcome.

Effect size calculations and analyses

Contrary to expectation, it was not possible to examine the incidence of POCD because the studies that provided these data used different criteria to define dysfunction, which would significantly impact on incidence rates (Slade, Sanchez, Townes, & Aldea, 2001). Effectively, the incidence rates from these studies were not comparable and could not meaningfully be meta-analysed (Cormack et al., 2012; Lipsey & Wilson, 2001).

Group data (means and SDs) were examined using Cohen's d effect sizes. When a study used a single-sample pre- and post-surgery design, a variant of Cohen's d (d_{RM}) was calculated (Lipsey & Wilson, 2001), with a negative d_{RM} indicating a decline in

cognitive performance between baseline and follow-up. When a two-sample (TJR and Controls) pre- and post-surgery design was used, an independent-groups repeated measures Cohen's d (d_{IGRM}) was calculated (Morris & DeShon, 2002). A negative d_{IGRM} indicates that there was a greater decline in cognitive performance between baseline and follow-up in the TJR group, compared to the controls or, alternatively, the cognitive performance of the Control group improved more than the TJR group when they were re-tested. A d_{RM} or d_{IGRM} of .2, .5 and .8 equates to a small, medium and large effect size, respectively (Cohen, 1988).

The reliability of an effect is influenced by its sample size, consequently it is recommended that the effect sizes from individual studies be weighted prior to calculating a mean effect. The inverse variance, which is the inverse of the squared standard error, is often used for this purpose but requires the correlation (r) between the baseline and follow-up scores(Lipsey & Wilson, 2001; Morris & DeShon, 2002). Unfortunately, no study reported these data. Three alternatives to r were identified: (1) published test-retest reliability coefficients (Lipsey & Wilson, 2001); (2) an estimate of r, based on the results of t-tests comparing pre- and post-surgery scores (Morris & DeShon, 2002); or (3) a single test-retest reliability coefficient for all tests, based on the minimum acceptable level of reliability (Lipsey, personal communication, 2012). The first two options were not possible because the data were not consistently available, either in the literature or individual studies, respectively; leaving only the third option. To this end, a test-retest reliability coefficient of .7, which is considered the minimum acceptable reliability coefficient for published psychological tests (Gregory, 2011), was used when calculating the weights for individual effect sizes.

Weighted mean effect sizes and ninety-five percent confidence intervals (95% CIs) were then calculated. If the 95% CIs include zero, it suggests that there is no significant

difference between the cognitive performance of the TJR group pre- and post-surgery (d_{RM}) or that there is no significant difference between the pre- and post-surgery test score changes of the TJR and controls groups (d_{IGRM}).

A random-effects model was used because there was heterogeneity among individual results and it was likely that a range of uncontrolled variables would impact on the effect sizes (e.g. demographic variables, specific surgical techniques, length of hospital admission) (Lipsey & Wilson, 2001). A random-effects model assumes that the effect sizes for individual studies vary due to both random error (unidentified sources of error) and normal sampling error, and weights individual effect sizes to counteract these two sources of error.

One limitation of meta-analyses is their susceptibility to publication bias, whereby significant results are more likely to be published, potentially skewing the findings of a meta-analysis (Lipsey & Wilson, 2001). Fail-safe N statistics (N_{fs}), which estimate the number of unpublished studies with non-significant results that would be required to reduce an effect to an inconsequential size (d = .1 for current purposes), were calculated to address this problem (Lipsey & Wilson, 2001). When the N_{fs} for an effect size was higher than $N_{studies}$, it was considered unlikely that there would be sufficient unpublished studies with non-significant findings to draw the current finding into question.

Effect sizes are reported for all tests that were used by at least two studies, either at the early (pre-discharge) or later (3-6 months post-surgery) follow-up interval, and were interpreted to suggest that POCD occurred following TJR if: (1) d_{RM} or $d_{IGRM} \leq -.2$ (i.e., at least a small negative effect, indicating decline); (2) the 95% CIs did not include zero (i.e., statistically significant effect); and (c) the $N_{fs} > N_{studies}$ (i.e., it was unlikely that there would be this number of unpublished studies with very small effects, relative to the number that had been published). As the d_{RM} measures change in the cognitive performance of TJR

patients over time and the d_{IGRM} measures whether the cognitive changes over time differed between patients and controls, the data for these two effect sizes are reported separately, as are the data for the pre-discharge and longer postoperative outcomes.

Results

Participants

The cognitive outcomes of 1,089 TJR patients and 89 healthy controls were assessed by 17 studies that were included in this meta-analysis. Summary demographic and surgical data for these samples are provided in Table 1, where it can be seen that the majority of participants were females, in their late-60s to mid-70s, who underwent total hip replacement. Unfortunately, too few studies provided data on marital status ($N_{studies}$ = 6), mean education ($N_{studies}$ = 8), pre-morbid IQ ($N_{studies}$ = 3), and co-morbid medical conditions ($N_{studies}$ = 7) to reliably report these sample characteristics.

Table 3-1: Summary demographic and surgery data for the total joint replacement and control groups

	TJR group					Control group				
	$N_{studies}$	$N_{participants}$	%	*M*	*SD*	$N_{studies}$	$N_{participants}$	%	*M*	*SD*
Sample size*	17	1089		64.1	54.6	2	89		44.5	16.3
Age (yrs)	14	873		71.6	3.4	2	89		72.9	1.5
Gender	14	979				89				
Female			63			2		57		
Male			37			2		43		
Surgery Type										
THR	8	640	59							
TKR	4	177	16							
THR/TKR	5	272	25							

Note. THR = total hip replacement, TKR = total knee replacement, $N_{studies}$ = number of studies, $N_{participants}$ = number of participants.
**Participants with complete baseline and follow-up data only.*

Early postoperative outcomes.

In total, 13 studies (NTJR = 807) examined cognitive functioning prior to being discharged from hospital (mean interval = 5.1 days, SD = 1.9) using a single-sample (TJR) pre- and post-surgery design. As seen in Table 2, the cognitive tests that were most frequently used were tests of immediate verbal recall ($N_{studies}$ = 7), Trail Making Tasks ($N_{studies}$ = 6), Controlled Oral Word Association Test ($N_{studies}$ = 6), and the Mini Mental Status Examination ($N_{studies}$ = 6).

Prior to discharge, TJR patients showed a small but significant negative effect for Choice Reaction Time performance, which suggests that they were slower to respond (refer to Table 2). However, this result is derived from only one study and should therefore be interpreted with caution. A moderate and significant negative effect was also evident for the Mini Mental Status Examination, indicating that patients typically performed more poorly on a commonly used cognitive screen shortly after surgery. In contrast, a moderate and significant improvement was found for delayed visual; however, this result was also only based on one study and may therefore be less reliable.

Interestingly, the majority of tests that were used at the pre-discharge assessment showed no discernable change in performance from the baseline testing that was performed prior to surgery. Specifically, within the memory domain, there was no change in immediate verbal recall, recognition memory, or delayed visual recall. In addition, no changes were observed for any of the attention or language tasks. Lastly, no significant change was noted for the tests of motor speed or digit substitution.

Table 3-2: Pre-discharge cognitive outcomes after total joint replacement surgery

Total joint replacement patient pre- and post-surgery data

Domain	*Test*	$N_{studies}$	$N_{participants}$	d_{RM}	*95% CI*		N_{fs}	*References*[c]
Memory	verbal - immediate recall	7	572	.10	-.10	.29	0	[5, 6, 12-14, 29, 37]
	verbal - delayed recall	5	236	-.18	-.39	-.03	4	[12-14, 29, 37]
	verbal - recognition	2	238	-.12	-.38	.12	1	[6, 13]
	visual - immediate recall	2	244	.01	-.08	.10	0	[6, 37]
	visual - delayed recall	1	22	.37*	.04	.70	3	[13]
Attention	Trail Making Task A	6	509	.03	-.10	.14	0	[5, 6, 12, 13, 29, 37]
	Trail Making Task B	6	509	-.05	-.20	.09	0	[5, 6, 12, 13, 29, 37]
	Digit Span	4	321	-.07	-.23	.08	0	[6, 13, 14, 29]
	WMS Attention & Concentration	1	28	.09	-.20	.38	1	[37]
Language	Controlled Oral Word Assoc. Test	6	509	.01	-.05	.08	0	[5, 6, 12, 13, 29, 37]
	Category fluency	3	251	.02	-.11	.08	0	[5, 12, 37]
	Boston Naming Test	2	277	.08	.00	.16	1	[6, 12]
Motor and Processing Speed	Choice Reaction Time	1	64	-.24*	-.40	-.08	1	[27]
	Motor speed	3	245	-.11	-.38	.17	1	[5, 12, 13]
	Substitution Task	3	400	-.26	-.54	.04	5	[5, 6, 13]
General Cognitive Screen	Mini-Mental Status Examination	6	216	-.41*	-.61	-.20	19	[17, 18, 27, 35, 36, 51]

Total joint replacement and Control participant pre- and post-surgery data

Domain	*Test*	$N_{studies}$	$N_{participants}$	d_{IGRM}	*95% CI*		N_{fs}	*References*[c]
Memory	verbal - immediate recall	2	309[a]	-.20	-.29	-.12	2	[5, 14]

Note. $N_{studies}$ = number of studies, $N_{participants}$ = number of participants, d_{RM} = weighted mean single-sample repeated measures Cohen's d, 95% CI = 95% confidence interval, N_{fs} = fail-safe N, d_{IGRM} = weighted mean independent-groups repeated measures Cohen's d, WMS = Wechsler Adult Memory
**satisfies criteria for change in performance ($d \geq .2$, CI ≠ 0, $N_{fs} > N_{studies}$)*
[a]*includes both TJR and Control participants*
[c]*corresponding references can be located in the reference list*

In contrast, there were only two studies (N_{TJR} = 220, $N_{controls}$ = 89) that assessed cognitive function prior to hospital discharge (mean interval = 5.5 days, SD = 2.1) using a two-sample (TJR and Controls) pre- and post-surgery design, with a verbal recall task being the one test that was used by both studies (refer to Table 2). A small, negative effect was found for this test, which suggests that the verbal recall of TJR patients improved less than the control participants between baseline (pre-surgery) and follow-up. However, the N_{fs} is low, suggesting that this finding may overestimate the true effect if publication bias has occurred. Although not evident from the data provided in Table 2, the raw data for these studies indicate that the TJR patients performed more poorly at both baseline and follow-up, compared to controls. Thus, the TJR patients had compromised verbal recall performance prior to surgery and this disparity increased in the early period after their surgery.

Longer-term postoperative outcomes.

A total of 12 studies (N_{TJR} = 970, $N_{controls}$ = 89) assessed cognitive function at longer follow-up (mean follow-up interval = 122.5 days, SD = 48.9) using a single-sample (TJR) pre- and post-surgery design. As seen in Table 3, the cognitive tests that were most commonly used by these studies were tests of immediate verbal recall ($N_{studies}$ = 8), Trail Making Tasks ($N_{studies}$ = 8), the Controlled Oral Word Association Test ($N_{studies}$ = 5), and digit substitution tasks ($N_{studies}$ = 5).

Table 3-3: 3-6 month cognitive outcomes after total joint replacement surgery

Total joint replacement patient pre- and post-surgery data

Domain	*Test*	$N_{studies}$	$N_{participants}$	d_{RM}	*95% CI*		N_{fs}	*References*[c]
Memory	verbal - immediate recall	8	656	.29*	.16	.42	15	[5, 6, 11-15, 37]
	verbal - delayed recall	4	216	.11	-.23	.45	1	[12-14, 37]
	verbal - recognition	2	301	.17	-.22	.57	1	[6, 13]
	visual - immediate recall	3	307	-.03	-.48	.43	0	[6, 14, 37]
	visual - delayed recall	2	85	.42*	.25	.59	7	[13, 14]
Attention	Trail Making Task A	8	653	.20	.11	.29	8	[5, 6, 10, 12-15, 37]
	Trail Making Task B	8	653	.18	.04	.32	6	[5, 6, 10, 12-15, 37]
	Digit Span	3	301	.07	-.08	.21	0	[6, 13, 14]
	WMS Attention & Concentration	2	89	.09	-.06	.23	0	[10, 37]
Language	Controlled Oral Word Assoc. Test	5	484	.09	-.01	.19	0	[5, 6, 12, 13, 37]
	Category fluency	3	246	.02	-.08	.12	0	[5, 12, 37]
	Boston Naming Test	2	277	.16	.11	.21	1	[6, 12]
Motor & Processing Speed	Choice Reaction Time	2	174	.15	.08	.21	1	[11, 15]
	Motor speed	4	283	.08	-.06	.22	1	[5, 12, 13, 15]
	Substitution Task	5	569	.28*	.16	.40	9	[5, 6, 11, 13, 15]
General Cognitive Screen	Mini Mental Status Examination	3	123	.00	-.38	.38	0	[18, 36, 38]

Total joint replacement and Control participant pre- and post-surgery data

Domain	*Test*	$N_{studies}$	$N_{participants}$	d_{IGRM}	*95% CI*		N_{fs}	*References*[c]
Memory	Immediate verbal recall	2	309[a]	.07	-.08	.22	0	[5, 14]
Attention	Trail Making Test A	2	309[a]	-.05	-.42	.32	0	[5, 14]
	Trail Making Test B	2	309[a]	.01	-.10	.12	0	[5, 14]

Note. $N_{studies}$ = number of studies, $N_{participants}$ = number of participants, d_{RM} = weighted mean single-sample repeated measures Cohen's d, 95% CI = 95% confidence interval, N_{fs} = fail-safe N, d_{IGRM} = weighted mean independent-groups repeated measures Cohen's d, WMS = Wechsler Adult Memory Scale
**satisfies criteria for change in performance ($d \geq .2$, CI ≠ 0, $N_{fs} > N_{studies}$)*
[a]*includes both TJR and Control participants*
[c]*corresponding references can be located in the reference list*

The TJR sample did not show evidence of deteriorating cognitive performance on any of the tests that were used; however, significant improvements were noted for three tests (refer to Table 3). Specifically, low-to-moderate positive effect sizes were found for the tests of immediate verbal and delayed visual recall, which suggests that the memory performance of the TJR patients improved when they were followed-up 3 to 6 months after their surgery. A small positive effect was also found for substitution task performance, indicating that processing speed improved.

As was seen for the pre-discharge results, there was no substantial change in performance on the majority of tests between baseline and the longer follow-up, as indicated by negligible effect sizes. More specifically, performance on specific tests of memory (delayed verbal recall, recognition memory, immediate visual recall), attention (Digit Span, Wechsler Memory Scale Attention and Concentration Index), language (Controlled Oral Word Association Test, Category Fluency, Boston Naming Test), speed (Choice Reaction Time, motor speed) and general cognition (Mini Mental Status Examination) all remained relatively constant.

Once again, two studies (N_{TJR} = 220, $N_{controls}$ = 89) assessed cognition at longer follow-up (3 months) using a two-sample pre- and post-surgery design, and tests of immediate verbal recall and Trail Making. No substantial effects were found for either of these measures, which suggest that any changes in performance between baseline and follow-up were comparable for the TJR patients and healthy controls (Table 3). However, consistent with the pre-discharge data, TJR patients performed significantly more poorly than controls on all tests at the baseline and longer follow-up interval, suggesting that the TJR patients were more cognitively compromised prior to surgery and remained so for three months post-surgery.

Discussion

The current meta-analysis investigated cognitive outcomes after TJR using data from 17 studies ($N_{patients}$ = 1,089), only two of which used a control group ($N_{controls}$ = 89). When followed-up prior to hospital discharge, the data for the TJR sample revealed small deficits in reaction time and general cognitive performance, compared to their pre-surgery performance. However, the majority of tests showed no change in performance, suggesting that TJR had minimal impact on cognitive performance within one week of surgery. Although the data were limited, when both TJR and control groups were assessed at baseline and pre-discharge, it was found that the immediate verbal recall of the TJR group was significantly poorer than that of the controls; a difference that was present prior to surgery but increased at the time of the pre-discharge follow-up. Pain and the use of opioid analgesics may partly explain the poorer pre-surgery performance of the TJR group (Chapman, Byas-Smith, & Reed, 2002; Duggleby & Lander, 1994)[. In addition, a small number of 'elective' surgeries may have involved revision procedures that were required due to infection, which may also impair cognition (Koessler & Pitto, 2002). The fact that the TJR patients showed evidence of poorer cognitive performance soon after surgery was not surprising, as they were likely to be experiencing high levels of pain and many more would be taking opioid analgesics, both of which impact on cognition (Chapman et al., 2002; Duggleby & Lander, 1994).

Data collected 3 to 6 months after TJR surgery may therefore be more informative with regard to POCD, as patients were likely to be experiencing less pain and unlikely to be taking high doses of opioid analgesics. However, based on the available data, there was no evidence of cognitive decline following TJR; rather, there were small-to-moderate improvements in immediate verbal recall, delayed visual recall and processing speed. Consistent with pre-discharge assessments, there were no changes in performance on the

majority of tasks. Finally, the two studies that assessed both TJR and control groups found that there were no differences in the changes to the immediate verbal recall and Trail Making performance of these groups over time. Thus, although the TJR patients performed more poorly at baseline, they remained equally compromised relative to their healthy peers three months after surgery. The poorer baseline performance of the TJR patients is likely to be the result of joint-related pain and the use of analgesia prior to undergoing surgery. However this does not explain why the differences continued when pain levels and the use of analgesics are likely to have decreased.

The large number of small and non-significant results in this study may, in part, be explained by the fact that a single conservative estimate of test-retest reliability (r = .7) was used to weight all effect sizes. This value is likely to have underestimated the reliability of some tests (Lezak et al., 2012) and, consequently, increased the size of the CIs and the likelihood that they would span zero, leading to the conclusion that there was no effect (Dunlap, Cortina, Vaslow, & Burke, 1996). Non-significant findings may also have resulted from the use of tests that are insensitive to subtle levels of cognitive decline, such as the MMSE (Friedman, Yelland, & R, 2011).

Alternatively, it is possible that TJR does not affect cognition. However, the failure to observe improvements in test scores due to repeated testing may itself indicate that there has been some cognitive deterioration that has been masked by practice effects (Lezak et al., 2012; Slade et al., 2001). While Control groups normally provide the means by which practice effects are measured and statistically controlled, there were only two studies that used control groups; neither of which showed evidence of improved performance with repeated testing. Unfortunately, these studies only used a small number of measures and so it is not known whether practice effects counteracted any decline on other measures.

It is also possible that cognitive decline occurred in a subset of individuals but was masked when group data was analysed (Murkin, Newman, Stump, & Blumenthal, 1995; S. P. Newman, 1995; Slade et al., 2001). This is illustrated in a recent meta-analysis of cognitive outcomes after cardiac surgery (Cormack et al., 2012) which, based on group data, concluded that there was either no change or small improvements in performance following surgery. However, the prevalence rates of those studies that provided group data, indicate that up to one third of cardiac patients showed cognitive decline; suggesting that there may be a subset of people who experience poor outcomes. This also appears to be the case for the current meta-analysis, with the group data indicating that there are either no persisting cognitive changes or small improvements after TJR surgery, and the prevalence rates for POCD varying between 16% and 45% (Deo et al., 2011; Evered, Scott, et al., 2011; Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011). For this reason, the *Statement of Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery* (Murkin et al., 1995) advocates monitoring the outcomes of individuals, as well as groups, when evaluating surgical interventions.

Finally, it is important to consider some of the limitations of this study. First, the data from different tests were combined for present purposes, which may have meant that tests that were subtly different (i.e. in terms of their sensitivity to cognitive deficits) were combined. Second, some studies assessed participants twice and others three times (pre-surgery + pre-discharge and/or 3-6 months), which may have affected the extent to which practice effects would be expected. Third, patients who were assessed between three and six months post-surgery were combined. Lastly, it was necessary to exclude three studies (Ancelin et al., 2010; Bickel et al., 2008; Kudoh et al., 2004) because they did not report the requisite data and attempts to obtain it were unsuccessful. This is particularly regrettable in the case of the Ancelin et al. (2010) study because it used a

sizeable cognitive test battery and a matched control group. The remaining two studies (Bickel et al., 2008; Kudoh et al., 2004) did not use a control group and only assessed cognition using the MMSE, and were therefore unlikely to add significantly to the findings.

Importantly, this meta-analysis highlights the need for additional good quality research, which uses an appropriate control group and clear criteria for identifying cases of POCD, in order to evaluate the frequency with which POCD occurs following TJR (Murkin et al., 1995). Demographically-matched healthy controls are likely to be the most viable option because they are readily available and control both for normal changes in performance over time and practice effects (Slade et al., 2001). However, a surgical control group is needed in order to determine whether TJR, as opposed to surgery itself, is responsible for any observed cognitive decline, provided that the surgical control and TJR groups are matched on important variables (e.g., demographic: age, education; surgical: type of and time under anaesthesia; and disability: pain, physical disability). Another option would be to use a control group consisting either of persons with osteoarthritis or who patients who are wait-listed for TJR surgery, provided they are comparable in terms of pain and disability (Slade et al., 2001).

Future research should also report both group and individual data. POCD must additionally be identified using sound theoretical and statistical methods, such as standardised regression-based methodology (Sawrie, Chelune, Naugle, & Lüders, 1996), which takes time-related confounds into consideration (e.g. practice effects, test-retest reliability, regression to the mean); therefore measuring 'true' change in individual patients. Lastly, it is important that researchers provide detailed information regarding other variables that may independently contribute to poor cognitive performance or other outcomes, such as the surgical method used (implant type, tourniquet vs no tourniquet),

anaesthetic (type, amount), medication (type, dosage, duration), level of pain, and depression.

In summary, prior to discharge, TJR patients showed no change in their performance on the majority of cognitive tasks from their pre-surgical assessment but there were small deficits in reaction time and general cognition. However, these assessments are likely to have been affected by postoperative pain and opioid analgesia. At the 3- to 6-month interval, the TJR group showed no change from baseline on the majority of tasks, although there were small improvements in immediate verbal recall, delayed visual recall, and speed of processing. Unfortunately, in the absence of adequate control data, it is not possible to more definitively determine whether TJR is associated with cognitive decline, as it is not known whether practice effects masked any such decline. Moreover, in the two studies where control groups were used, it appeared that TJR patients were cognitively compromised even before surgery, which further complicates the picture. Additional methodologically rigorous research into POCD after TJR is needed if we are to gain a better understanding of the incidence, cause and impact of POCD.

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Appendices

Search terms used

Total Joint Replacement	**Cognition**
“joint replacement”	“cogniti*”
“hip replacement”	“neurocog*”
“knee replacement”	“neuropsycholo*”
“joint surgery”	“neurobehavioural”
“hip surgery”	“mental performance”
“knee surgery”	“mental capacity”
“joint procedure”	“mental function”
“hip procedure”	“mental competenc*”
“knee procedure”	“mental ability*”
“joint prosthesis”	“psychologic*”
“hip prosthesis”	
“knee prosthesis”	
“arthroplasty”	
“TJR”	
“THR”	
“TKR”	
“THA”	
“TKA”	

Chapter 4. Study 2

Incidence of delirium following total joint replacement in older adults: A meta-analysis.

This chapter presents a published paper, the details of which are:

Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2015). Incidence of delirium following total joint replacement in older adults: A meta-analysis. *General Hospital Psychiatry, 37*, 223-229. doi:10.1016/j.genhosppsych.2015.02.004

Statement of Authorship

Statement of Authorship

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Contribution to the Paper	Conducted literature searches, coded articles, analysed and interpreted data, wrote manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Prof Jane Mathias		
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Preface

As noted in Chapter 1, it is well established that TJR patients are susceptible to delirium; however, a wide range of incidence rates have been reported. As there are many predisposing and precipitating factors for delirium, the risk may vary between-samples. Furthermore, differences in how delirium is measured may contribute to some of this variation. The current meta-analysis therefore evaluated the literature that has investigated the incidence of delirium after TJR. The main aim was to determine the overall incidence of delirium after TJR and to examine whether it varied according to differences in patient characteristics (e.g. hip/knee surgery; included/excluded patients with pre-existing cognitive impairment) and study methodology (e.g. delirium assessment instrument; frequency of assessment).

Abstract

Objective: Delirium is common in older adults following total joint replacement (TJR) of the hip and knee. However, reports of the incidence of delirium vary widely, limiting their usefulness. The current meta-analysis therefore examined (1) the incidence of delirium in older patients who underwent TJR and (2) whether these rates vary according to the (a) joint (hip/knee replacement), (b) inclusion/exclusion of patients who underwent simultaneous bilateral surgery, (c) inclusion/exclusion of patients with pre-existing cognitive impairments, (d) type of anaesthesia (regional/general), (e) method/frequency of assessment, and (f) postoperative interval.

Method: Data from24 studies (2,895 patients) that measured post-surgical delirium following TJR were analysed. Mean weighted proportions were calculated using a random-effects model to assess the overall incidence of delirium and whether the rate varied according to the aforementioned variables.

Results: Overall, 17% of patients who underwent TJR developed delirium during hospital admission. Individual estimates varied from0% to 82%, but this variability was not adequately explained by the variables that were examined.

Conclusions: Delirium is relatively common following TJR; however, it remains unclear why individual estimates vary so widely. Health professionals working with these patients should remain alert to the presentation, diagnosis and management of delirium to optimise post-surgical outcomes.

Delirium involves disturbances in attention, awareness and other cognitive abilities, and is characterised by a sudden onset and symptoms that fluctuate throughout the day (American Psychiatric Association, 2013). Approximately 30% of medical inpatients (Martins & Fernandes, 2012), 60% of surgical patients, and 80% of intensive care patients (O'Regan, Fitzgerald, Timmons, O'Connell, & Meagher, 2013) develop delirium during their hospital stay. While the causes remain controversial, delirium has been associated with a variety of predisposing factors, including older age, dementia, multiple medical co-morbidities, and polypharmacy (Inouye, 2006). In addition, precipitating factors include pain, lack of environmental stimulation, specific medications (e.g. sedatives, anticholinergic drugs), dehydration (Inouye, 2006) and certain medical conditions, such as urinary tract infections (Eriksson, Gustafson, Fagerström, & Olofsson, 2011) and obstructive sleep apnea (Mirrakhimov, Brewbaker, Krystal, & Kwatra, 2013).

Delirium is especially common among intensive-care patients (Ouimet, Kavanagh, Gottfried, & Skrobik, 2007) and those admitted for emergency surgery (Galanakis, Bickel, Gradinger, Von Gumppenberg, & Forstl, 2001), possibly because they possess multiple risk factors (e.g., older age (Parker & Johansen, 2006), dementia, chronic illnesses (Ely et al., 2001), greater pain (Vaurio, Sands, Wang, Mullen, & Leung, 2006), acute trauma (Inouye, 2006). Patients who undergo *elective* surgery, such as total joint replacement (TJR) of the hip or knee, are also susceptible (Bruce, Ritchie, Blizard, Lai, & Raven, 2007; Flink et al., 2012; Jankowski et al., 2011), despite the relatively predictable peri-operative course (Talmo, Robbins, & Bono, 2010), the presence of fewer risk factors, (Schor et al., 1992), and the relatively good health of these patients (elective procedures are generally contraindicated if major comorbid conditions are unstable or poorly managed).

Importantly, post-surgical delirium increases the risk of a person experiencing poorer cognitive and functional outcomes, even after controlling for age, co-morbid

conditions and pre-surgical cognitive status (Bickel, Gradinger, Kochs, & Forstl, 2008; Duppils & Wikblad, 2004b; McCusker, Cole, Dendukuri, Han, & Belzile, 2003). Furthermore, delirium may have significant financial implications for both the patient and the broader health sector; in part due to the extended hospital admissions that are associated with this diagnosis (Kat et al., 2008; Leslie, Marcantonio, Zhang, Leo-Summers, & Inouye, 2008; Ouimet et al., 2007; Siddiqi, House, & Holmes, 2006; Witlox et al., 2010). At present, however, there is limited data regarding the outcomes of older patients who underwent TJR and who developed post-surgical delirium, although the available research suggests that these patients may similarly be at risk (Bickel et al., 2008; Duppils & Wikblad, 2004b).

Given the associated burden of delirium, it is important to consider its incidence among patients who undergo TJR. A meta-analysis of research examining delirium following elective orthopaedic surgery reported that approximately 9% to 12% of patients developed post-surgical delirium (Bruce et al., 2007)[14]. However, more recent studies that used TJR-specific samples have reported rates of delirium between 0% (Krenk et al., 2012) and 48% (Kinjo, Lim, Sands, Bozic, & Leung, 2012). Such variability limits the clinical utility of this data when trying to determine the risk of delirium after TJR.

Differences in the samples and methodologies used to investigate delirium may contribute to some of this variability (Bruce et al., 2007). Specifically, the inclusion of patients who have been diagnosed with dementia (Bruce et al., 2007), have undergone simultaneous bilateral replacements (Lynch, Trousdale, & Ilstrup, 1997), and/or had general, rather than regional, anaesthesia (Hole, Terjesen, & Breivik, 1980) may all lead to higher rates of delirium. In addition, the measures used to assess delirium may vary in their sensitivity (Bruce et al., 2007), with the qualifications and experience of the staff who perform these assessments also potentially impacting on the reported incidence of

delirium (Inouye, Foreman, Mion, Katz, & Cooney, 2001). Lastly, patients who are assessed more frequently and over a longer period of time may have higher rates of delirium because it is more likely to be detected (Bruce et al., 2007).

Given the frequency of TJR surgery (Australian Orthopaedic Association National Joint Replacement Registry, 2012) and the fact that delirium is known to be associated with poorer outcomes (Witlox et al., 2010), it is important to determine how frequently delirium occurs following TJR. Based on research with similar clinical samples, it is likely to be common and to be affected by many of the aforementioned variables. The current meta-analysis therefore examined the overall reported incidence of delirium after TJR, and whether this rate differed according to: the type of surgery (hip or knee replacement), the pre-surgical cognitive status of patients (i.e., inclusion or exclusion of patients with dementia), whether patients who underwent simultaneous bilateral surgery were included, whether general or regional anaesthesia was used, the method (measure of delirium, professional assessing delirium) and frequency of assessment, and the post-surgical assessment interval.

Method

Search strategy and research design.

The Pubmed, PsycINFO, Embase, and Scopus electronic databases were searched using a broad range of terms to identify original studies, published between January 1980 and January 2014 that screened TJR patients for delirium (see Appendix A, Supplementary Materials for search terms). The reference lists of reviews that examined TJR and delirium were also searched to identify further studies.

To be eligible for inclusion, studies needed to have: (1) assessed patients who had undergone elective TJR of the hip or knee and received 'standard care' (i.e. did not receive any experimental treatment); (2) examined participants who were 50 years of age or more (based on age range or mean age minus 1 SD ≥ 50 years); (3) screened for post-surgical delirium using either Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association, 2013) or International Classification of Disease (World Health Organization, 1992)[31] criteria, or a published delirium-specific screening tool (e.g. Confusion Assessment Method; Inouye et al., 1990); (4) reported prevalence data or provided data from which an effect size could be computed (e.g. number of cases); (5) had a sample size >1 (i.e., excludes case studies); and (6) been published in English in a journal. Data from studies that evaluated an experimental surgical procedure were only eligible if there was a 'standard care' TJR group. Studies were also deemed eligible if patients underwent 'elective' hip or knee replacement surgery because, although this may refer to partial/revision/total joint replacement, the majority of elective joint procedures involve TJRs (72% - 96%; Australian Orthopaedic Association, 2010; Canadian Joint Replacement Registry, 2012; Garellick, Karrholm, Rogmark, & Herberts, 2010). Three studies (Andersson, Gustafson, & Hallberg, 2001; McCaffrey, 2009; Wong, Wong, & Brooks, 2002) reported 'elective hip/knee surgery,' but did not specify whether patients underwent replacement procedures, as opposed to other forms of elective surgery (e.g. arthroscopy), therefore the authors were contacted for confirmation. Two authors responded (McCaffrey, 2009; Wong et al., 2002) and these studies were subsequently included. Studies were excluded if they recruited an elective 'orthopaedic' sample (Litaker, Locala, Franco, Bronson, & Tannous, 2001; Marcantonio et al., 1994), because these studies may include other types of surgery (e.g., shoulder). Finally, studies were excluded if prevalence data were based on informal assessments, such as entries in

medical files by staff who were not specifically instructed to assess delirium (Petruccelli, Rahman, de Beer, & Winemaker, 2012). These data were considered less reliable because delirium may not have been a primary concern and, without specific training, symptoms may not be recognised (Inouye et al., 2001; Rice et al., 2011).

The original search located 1,359 studies, excluding duplicates (for full details see the Supplementary Materials, Figure A). An examination of all titles and abstracts revealed that 197 papers were potentially eligible and warranted further attention. The full-text versions of these studies were therefore retrieved. One hundred and ten of these papers were subsequently excluded on the basis of ineligible methodologies (e.g., data collected retrospectively from medical records) or samples (e.g., aged under 50), unusable data, or a combination of factors. In total, 29 studies met all of the inclusion criteria. The reference lists of twenty reviews were also examined: one additional study (Lynch et al., 1998) was located using this method, increasing the number to 30 studies.

Lastly, these studies were screened to ensure that all samples were independent of one another. Three studies by both Cerejeira et al. (2011; 2013; 2012) and Dupplis et al. (2000, 2004a, 2004b), and two by Lowery et al. (2007; 2008), used non-independent samples. In addition, sample independence of two studies by Kudoh et al. could not be confirmed (Kudoh, Takase, Takahira, & Takazawa, 2004; Kudoh, Takase, & Takazawa, 2004). The data for these authors were therefore combined, leaving a total of 24 independent studies in the final review.

Effect size calculations and analyses.

Most data were reported as proportions ($N_{studies}$=23) - which are an effect size in themselves (Lipsey & Wilson, 2001) - indicating the rate with which patients developed delirium following TJR during their hospital admission. One study provided means and

SDs, but met all of the other inclusion/exclusion criteria (McCaffrey, 2009). Incidence data was therefore requested via email, which the corresponding author provided. All effect size calculations and analyses were conducted using Comprehensive Meta-Analysis software (Biostat, Englewood New Jersey). A random-effects model, which assumes that effect sizes vary as a consequence of both sampling error and methodological differences (Card, 2012; Lipsey & Wilson, 2001), was used to calculate mean effects. The proportions obtained from individual studies were weighted by sample size, and combined to calculate mean effect sizes (mean proportions), for which 95% confidence intervals (CIs) were computed. 95% CIs that do not include zero indicate that the population prevalence is significantly different from zero. All mean effect sizes and CIs were expressed as percentages, and a forest plot of the individual and mean percentages, together with 95% CIs were created using the Forest Plot Viewer software (National Toxicology Program, North Carolina; Boyles A.L., Harris S.F., Rooney A.A., & Thayer K.A., 2011). A funnel plot was used to assess the potential for publication bias, which refers to the over-representation of statistically significant results within the published literature. The logit-transformed proportions for individual studies were plotted against their standard errors, with a line in the middle representing the mean effect size. The individual study 'plots' form a symmetrical funnel shape around the mean effect size when publication bias is unlikely. An asymmetrical funnel, on the other hand, may indicate publication bias (Cumming, 2012).

A number of analyses were performed to determine whether a selection of sampling and methodological variables were associated with some of the variation in the rates of delirium. First, the overall incidence of delirium following TJR was examined, after which separate rates were calculated for those undergoing hip and knee replacements, and for studies that included or excluded patients who underwent simultaneous bilateral

procedures. Next, study data were examined in terms of whether they included or excluded patients who had pre-existing cognitive impairments. The 'unselected' group comprised studies that did not exclude participants on the basis of pre-surgical cognitive status (i.e., potentially included people with dementia/cognitive impairment) and the 'no impairment' group included studies that either excluded cognitively impaired participants or reported post-hoc that there were no such participants. Two studies (Duppils & Wikblad, 2000; Williams-Russo et al., 1999) only excluded those participants with very low Mini Mental Status Exam Scores (<11), and two excluded patients who could not give informed consent (Galanakis et al., 2001; Lynch et al., 1998), which meant that persons with mild or moderate cognitive deficits may have been included in these studies. As a result, these studies were included in the 'unselected' group. In addition, data were examined in an attempt to assess whether any of the following variables had a significant impact on the reported incidence of delirium: (1) the type of anaesthesia used (general or regional); (2) the specific delirium assessment instrument used; (3) the profession of the person who conducted the delirium assessment(s) (e.g. psychiatrists, nurses, multi-disciplinary researchers); (4) the frequency of screening for delirium; and (5) the duration of postoperative delirium screening following TJR.

Results

Data from 24 studies, which screened for delirium in 2,895 patients who underwent TJR, were analysed. As seen in Table 1, most patients were females between the ages of 70 and 79. Over half of the patients came from studies that examined mixed samples of hip and knee replacements, with studies of hip replacement being more common than knee replacement. Approximately 50% of studies reported the type of anaesthesia that

was used during surgery. Of these, 52% reported on mixed samples who underwent either general or regional anaesthesia, 30% used regional anaesthesia alone, and 18% only used general anaesthesia. Unfortunately, too few studies reported comparable information relating to co-morbid medical conditions ($N_{studies}$=3) to report or analyse here.

Table 4-1: Summary of demographic and surgical details for total joint replacement patients

	$N_{studies}$	$N_{participants}$	%	*M*	*SD*
Sample size	24	2895		120.6	94.8
Age (yrs)	16	1868		72.9	3.1
Gender	15	1891			
Female			61.9		
Male			38.1		
Surgery Type	24	2895			
Total hip replacement			33.1		
Total knee replacement			8.2		
Both			58.7		
Anaesthetic	12	1847			
General			17.8		
Regional			29.8		
General/Regional			52.4		

Note. $N_{studies}$ = number of studies, $N_{participants}$ = number of participants, M = mean, SD = standard deviation

Overall, 17.3 % of patients who underwent TJR developed delirium during their hospital admission (refer to Figure 1). There was considerable variation in the rates reported by individual studies (0% to 81.1%), although most fell between 10% and 30%. A funnel plot of these effect sizes revealed a slightly asymmetrical distribution (see Figure 2), with fewer studies reporting above average delirium rates (right-side of plot). Approximately three more studies, with above average rates, would be needed to make the plot symmetrical (shown as black dots in Figure 2). Importantly, these findings do not provide evidence of publication bias because there was no shortage of smaller effects (below the mean).

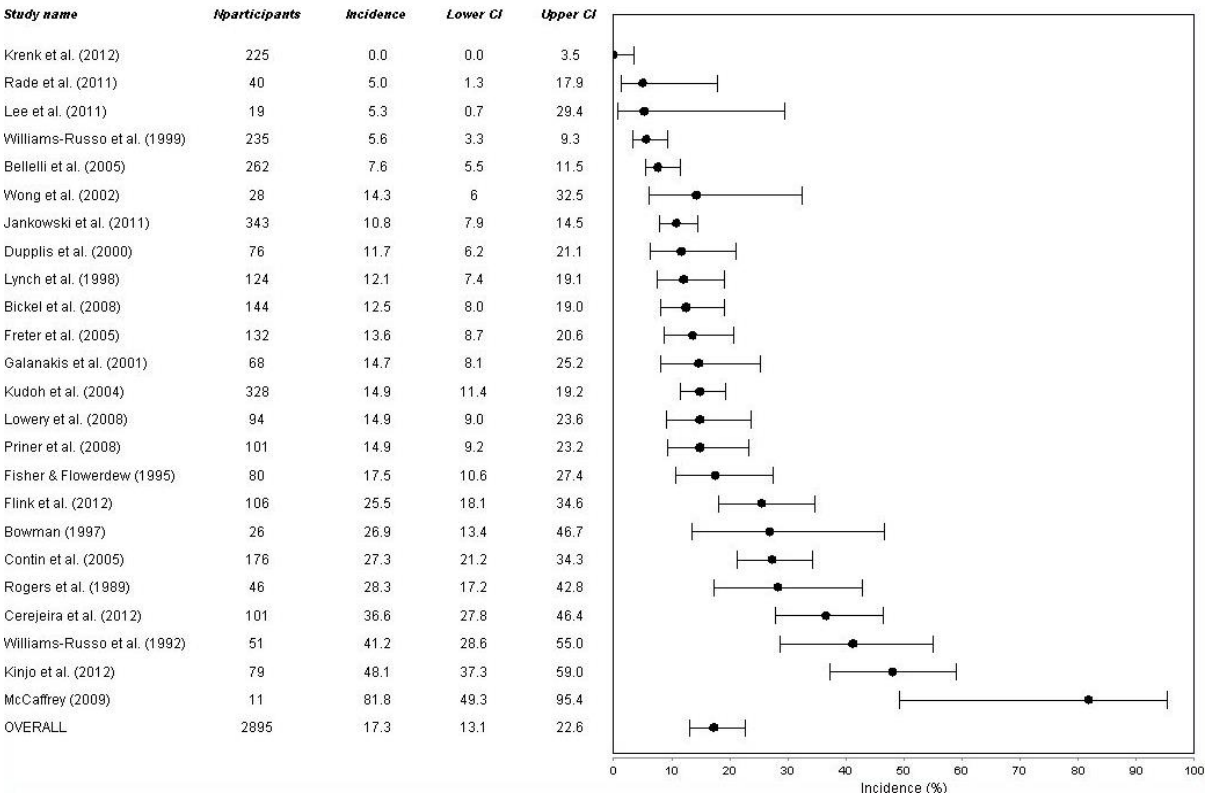

Figure 4 1: Individual study and mean incidence of delirium after total joint replacement

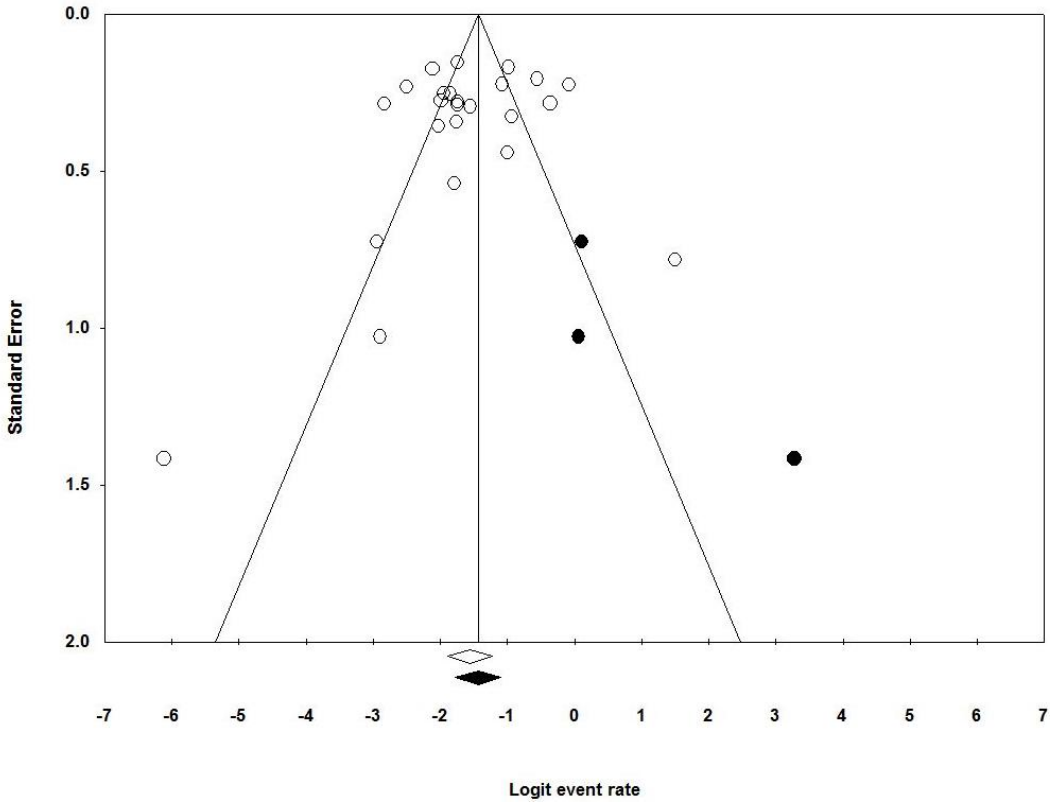

Figure 4 2: Funnel plot of observed and imputed individual logit effect size.
Note: Black dots represent imputed effects sizes, which are required to make the distribution symmetrical
s

A total of nine studies exclusively recruited patients with hip replacements and three with knee replacements. The remaining eleven studies examined mixed samples of hip and knee replacements, of which seven provided separate data for both subgroups (Contín, Perez-Jara, Alonso-Contín, Enguix, & Ramos, 2005; Jankowski et al., 2011; Krenk et al., 2012; Lynch et al., 1998; Priner et al., 2008; Rade, Yadeau, Ford, & Reid, 2011; Rogers et al., 1989) and one provided data for patients who underwent knee replacement surgery (Kudoh, Takase, Takahira, et al., 2004). As seen in Table 2, patients who received a hip replacement had a slightly lower incidence of delirium than those who had a knee replacement; however, this difference was not significant (i.e. 95% CIs overlap).

The inclusion/exclusion of patients undergoing bilateral replacements was also of interest. However, only six studies provided these details and only one included patients who underwent simultaneous bilateral surgery. Therefore, this variable could not be reliably assessed in a meaningful way.

Next, studies were sorted into two groups in order to determine whether the pre-surgical cognitive status of the sample was associated with differences in delirium rates: 'unselected' ($N_{studies}$=9) and 'no impairment' ($N_{studies}$=14). Notably, the mean rates of delirium for the 'unselected' and 'no impairment' groups did not differ significantly (refer to Table 2).

Only 12 studies provided information relating to whether they used general or regional anaesthesia. Of these, one study exclusively used general anaesthesia (Kudoh, Takase, Takahira, et al., 2004), four used regional anaesthesia (Krenk et al., 2012; Rade et al., 2011; Williams-Russo et al., 1999; Williams-Russo, Urquhart, Sharrock, & Charlson, 1992), and seven used either general or regional. Three of these latter seven studies

(Cerejeira et al., 2012; Contín et al., 2005; Flink et al., 2012) provided separate data for their general and regional anaesthetic subgroups, which were combined with the other general or regional data. As seen in Table 2, delirium was slightly more common when general anaesthesia was used; however, this difference was not significant (i.e., overlapping CIs).

Delirium was most frequently assessed using either the Confusion Assessment Method (CAM; Inouye et al., 1990) ($N_{studies}$=14) or DSM criteria (DSM-III, DSM-IV; American Psychiatric Association, 1980, 1994); $N_{studies}$=7), which yielded highly comparable rates (refer to Table 2). The NEECHAM Confusion Scale gave a significantly higher rate (81.8%), but was only used with one very small sample whose cognitive status was not reported. The remaining two studies each used either the Korean Delirium Rating Scale 98, or the Delirium Rating Scale 98 in conjunction with DSM criteria and reported rates of 5.3% and 25.5%, respectively.

Delirium was typically assessed by nurses ($N_{studies}$=6), researchers from a range of disciplines ($N_{studies}$=8), or psychiatrists ($N_{studies}$=3). The remaining seven studies used a variety of assessors, relied on multiple professionals to reach a consensus diagnosis, or did not specify who conducted the assessment and were therefore grouped together ('other'). Psychiatrists identified a higher rate of delirium, compared to nurses and researchers (see Table 2); however these differences were not significant.

Lastly, the impact of the frequency of assessment and postoperative interval on the reported rates of delirium were examined (see Table 2). Most studies assessed delirium once daily ($N_{studies}$=14), with many fewer performing multiple assessments in a single day ($N_{studies}$=5). A further three studies assessed patients at least once daily (Kudoh, Takase, Takahira, et al., 2004; Williams-Russo et al., 1999; Williams-Russo et al., 1992) and two

did not specify (Bellelli, Speciale, & Trabucchi, 2005; Flink et al., 2012). The incidence of delirium was higher, albeit not significantly, in those studies that assessed delirium once daily, compared to studies that performed multiple assessments. Finally, studies were grouped according to their postoperative interval into either 1-2 days ($N_{studies}$=7) or three or more days ($N_{studies}$=16). Studies that reported completing 'daily' assessments were included in the latter group, as they were assumed to have conducted assessments each day of admission, which is usually more than two days. The data indicate that the incidence of delirium was higher among the studies that assessed patients on one or two days after their surgery compared to studies that assessed patients on three or more days postoperatively (refer to Table 2).

Table 4-2: Incidence of delirium during hospital admission for total joint replacement

Test	$N_{studies}$	$N_{participants}$	P_M	*95% CI*		*References*[e]
Sample characteristics						
Surgery type						
Hip replacement	16[a]	1500	12.5	8.4	18.1	[8, 13, 17, 24, 38, 43, 45, 47, 58-62, 64-66]
Knee replacement	11[b]	900	20.3	12.8	30.5	[12, 13, 24, 25, 43, 52, 59-63]
Cognitive status						
Unselected	9	1135	13.8	10.7	17.6	[8, 43, 47, 51, 62, 64, 66-68]
No impairment	14	2026	17.9	11.9	26.0	[12, 13, 17, 24, 25, 38, 45, 49, 58-61, 63, 65]
Anaesthesia type						
General	4[c]	497	19.5	9.4	36.3	[12, 45, 51, 59]
Regional	7[d]	929	15.7	8.0	28.6	[12, 24, 45, 58, 59, 61, 63]
Methodological variables						
Assessment measure						
CAM	14	1924	15.6	11.2	21.4	[8, 13, 17, 25, 38, 43, 45, 49, 51, 60, 61, 64, 67, 68]
DSM criteria	7	881	16.7	8.4	30.3	[24, 47, 58, 59, 62, 63, 65]
K-DRS-98	1	19	5.3	0.7	29.4	[66]
DRS-R-98/CAM	1	106	25.5	18.1	34.6	[12]
NEECHAM Confusion Scale	1	11	81.8	49.3	95.4	[37]
Assessor						
Nurse	6	1201	14.2	8.9	21.9	[13, 24, 38, 51, 59, 60]
Researcher	8	607	22.7	12.3	38.0	[25, 37, 43, 47, 49, 61, 63, 68]
Psychiatrist	3	166	27.8	15.7	44.5	[45, 62, 66]
Other	7	921	13.8	8.7	21.2	[8, 12, 17, 58, 64, 65, 67]
No. of daily assessments						
Once daily	14	1299	21.8	15.7	29.6	[8, 17, 25, 37, 38, 43, 45, 49, 59, 60, 62, 65, 66, 68]
At least once (≥ 1 daily)	3	614	16.2	5.6	38.4	[51, 58, 63]
More than once daily	5	764	9.9	5.6	16.8	[13, 24, 47, 61, 67]
Not specified	2	368	14.4	4.0	40.4	[12, 64]
No. of days assessed postoperatively						
1-2 days	7	576	27.7	20.0	37.1	[12, 25, 38, 45, 59, 61, 62]
3 or more days	16	2057	15.0	11.2	20.0	[8, 13, 17, 24, 37, 43, 47, 49, 51, 58, 60, 63, 65-68]

Note: $N_{studies}$ = number of studies, $N_{participants}$ = number of participants, P_M = weighted incidence, 95% CI = 95% confidence interval, N_{fs} = fail-safe N, CAM = Confusion Assessment Method, DSM = Diagnostic Statistical Manual (3rd, 4th ed.), K-DRS-98 = Korean version of the Delirium Rating Scale-Revised-98, DRS-R-98 = Delirium Rating Scale-Revised-98.

[a] *includes only hip replacement patients from [24, 43, 59-62]*

[b] *includes only knee replacement patients from [24, 43, 52, 59-62]*

[c] *includes only general anaesthesia patients from [12, 45, 59]*

[d] *includes only regional anaesthesia patients from [12, 45, 59]*

[e] *corresponding references can be located in the reference list*

Discussion

The current meta-analysis synthesised data from 24 independent studies that assessed the incidence of delirium following TJR surgery ($N_{participants}$=2,895 TJR patients). Although the rates reported by individual studies varied substantially (0%-82%), an average of approximately one in six people aged over 50 develop delirium during their hospital admission (17%). This rate is comparable to elderly patients who present to the emergency department (Martins & Fernandes, 2012), but is slightly lower than persons seen in intensive care units (Ouimet et al., 2007) and those who have suffered a hip fracture (Bruce et al., 2007), or have undergone cardiac surgery (O'Regan et al., 2013). This may reflect the notion that patients who undergo TJR may have fewer risk factors for delirium (Inouye, 2006) compared to these other patient groups.

As rates of delirium varied substantially, this meta-analysis examined differences in the samples that were recruited and the methodologies that were used in an effort to explain this variability. The current findings indicate no significant difference in the rate of delirium between hip and knee replacement patients. In addition, these findings indicate that the pre-surgical cognitive profile of the sample – namely, whether they included or excluded patients with cognitive impairment – did not account for differences in the incidence of delirium. Instead, the rates of delirium were highly comparable between the two groups. This is consistent with an earlier analysis of elective orthopaedic patients by Bruce et al. (Bruce et al., 2007) who reported minimal differences in the rates of delirium for samples with and without cognitive impairments. Using base-rates for the general population (American Psychiatric Association, 2013), the 'unselected' sample is likely to

have included a small number of patients with dementia, which may have been too few to impact on the risk, and therefore the incidence, of delirium. The prevalence of dementia within these 'unselected' samples may also vary, with the older samples (e.g., >70 years) potentially including more people with dementia. The impact of general versus regional anaesthesia was also investigated. Consistent with previous research in this area (Mason, Noel-Storr, & Ritchie, 2010), there was no difference in the rate of delirium for patients who underwent general versus regional anaesthesia.

Similarly, various methodological variables were found to have minimal impact on the incidence of delirium. The two main methods of assessment - the CAM and DSM - yielded comparable rates, while the NEECHAM, which was only used with one very small sample, yielded a much higher and potentially unreliable estimate; suggesting that it should be regarded as an outlier. Removal of this study reduced the mean rate of delirium slightly from 17.3 to 16.3 (95% CIs = 12.3 to 21.3). In addition, there was a trend toward higher rates of delirium when researchers and psychiatrists performed the assessment, although, once again, this difference was not significant. This finding is consistent with previous research among other samples showing that delirium may be under-reported by nurses (Inouye et al., 2001; Rice et al., 2011), potentially due to the many competing demands on their time and expertise. As delirium can fluctuate over time, it was expected that studies that performed multiple assessments within or across days, would yield higher rates. Somewhat surprisingly, there was no difference in the delirium rates of studies that performed assessments once daily or multiple times in a day. However, studies that assessed patients on one or two days after their surgery reported a *higher* rate of delirium compared to studies that assessed patients on three or more days postoperatively. The reason for this is unclear: additional information relating to the exact number and timing of assessments is needed to clarify.

Overall, despite examining a number of variables, this analysis failed to identify clear reasons for the substantial variation in the incidence of delirium reported by different studies. Indeed, there was considerable variability (evident in the 95% CIs) in the findings of studies that were ostensibly methodologically similar, suggesting that there are other candidate variables that could not be investigated here due to insufficient data. Older age, for example, may increase the risk of delirium (Inouye, 2006). However, this could not be investigated due to inconsistencies in how these data were reported, with some studies reporting mean ages and others an age range. Some of the variation may also be due to hospital-specific differences in patient profiles or patient care (Bruce et al., 2007). For example, samples drawn from hospitals in low socioeconomic areas may have a higher prevalence of diabetes (Jaffiol, Thomas, Bean, Jégo, & Danchin, 2013), which is a risk factor for delirium (Lin, Chen, & Wang, 2012). Alternatively, the hospital environment may vary. For instance, patients may be moved between rooms – a practice that may vary between hospitals (Bellelli et al., 2005) – which may cause them to become disorientated, possibly increasing their risk of delirium (McCusker et al., 2001). Indeed, there are numerous other risk factors for delirium, many of which are subtle (e.g. a clock in the room lowers the risk; McCusker et al., 2001), making it difficult for studies to report on all of these variables. Lastly, the current studies were published over a 24-year period, during which there have been substantial advances in peri-operative care (e.g. early mobilisation) for patients who undergo TJR, which have resulted in shorter hospital admissions. Patients from more recent studies may, therefore, been at a lower risk of delirium due to these advances. However, when we examined this possibility using the available data, we failed to find a relationship between publication date and the incidence of delirium, suggesting that a more detailed analysis of variables related to peri-operative care is needed to properly evaluate the impact of any such improvements. Overall, it remains

difficult to define the specific reasons for the disparate estimates of delirium following TJR. Finally, it may be that there is no 'true' incidence of delirium. Rather, delirium may be a heterogeneous disorder, with rates that differ according to patient demographics and aspects of in-hospital care (Bruce et al., 2007).

Turning to the limitations of this study, it is possible that the samples recruited for the primary studies were not broadly representative of the TJR population. Most studies excluded patients with cognitive impairments, potentially due to issues relating to informed consent. Cognitively impaired patients are therefore likely to be under-represented in this analysis (Young & Inouye, 2007), the impact of which is unclear. Second, delirium is difficult to diagnose, often being misdiagnosed as depression, panic disorder, schizophrenia (Breitbart & Alici, 2008) or dementia (Cole, 2004; Young & Inouye, 2007), which may mean that the true rate (if it exists) is higher than reported here. Third, the symptoms of delirium fluctuate, often worsening at night (Cole, 2004), and may be missed if assessments are only performed on a daily basis. Ideally, multiple assessments performed throughout the day and night, would reduce the potential for under-diagnosis (Martins & Fernandes, 2012). However, this is likely to be impractical in many clinical settings. Specialised training in the assessment of delirium may also be required, as this is known to be an area where medical professionals lack confidence and knowledge (Davis & MacLullich, 2009; Inouye et al., 2001; Kennelly et al., 2012; Rice et al., 2011). Fourth, it was not possible to evaluate the severity or course of delirium because too few studies provided this information. Consequently, patients who experienced a single period of delirium were combined with those who fluctuated between delirium and lucidity throughout their admission. Ideally, these categories should be considered separately, as they may differ in terms of their risk factors, management and prognosis. Fifth, there were two studies that were included in a previous meta-analysis (Bruce et al., 2007) but were

not included here. One could not be located and appears to be a conference abstract (Silverstein, 1999), and a second was not published in English (Linstedt, Berkau, Meyer, Kropp, & Zenz, 2002) and, therefore, did not meet one of the inclusion criteria. In addition, one study was excluded because they did not specify whether the sample underwent joint 'replacement' surgery, as opposed to other elective hip or knee procedures (Andersson et al., 2001). However, given the characteristics of their sample (older adults with a diagnosis of osteoarthritis), it is likely that these studies largely assessed patients who underwent TJR. Finally, this meta-analysis was limited as it could only look at variables that are potentially associated with the development of delirium in isolation of one another. Multivariate analyses, which can assess the interaction of different variables, could not be performed due to the limited research in this field.

Future research on delirium following TJR should endeavour to provide additional data relating to variables that may influence post-surgical outcomes, such as age, pre-surgical cognitive status and co-morbid medical conditions (e.g., diabetes, depression, atrial fibrillation), which are all risk factors for delirium (Lin et al., 2012). The types and numbers of medications should also be reported. Surgical details, such as whether bilateral procedures were performed and the type of implant, are additionally needed because patients who undergo cemented (as opposed to uncemented) total hip replacement are reportedly at greater risk of embolization and neurological problems (Issack, Lauerman, Helfet, Sculco, & Lane, 2009). The rate and nature of medical complications, such as urinary tract infections, which can predispose a person to developing delirium (Young & Inouye, 2007), should also be reported. Similarly, the type and method of administering analgesics can influence patient outcomes, with patient-controlled intravenous administration of analgesics reportedly increasing the risk of delirium (Vaurio et al., 2006). Where possible, cases of delirium should be stratified

according to patient and surgical factors, and multivariate analyses should be used to assess the interplay between a range of different variables. Such detail may improve our understanding of the risk factors for developing delirium following TJR. Moreover, research is needed to evaluate the relationship between delirium and post-surgical outcomes, and whether relatively simple delirium prevention measures - such as peri-operative geriatric consultations (Moyce, Rodseth, & Biccard, 2014) - improve outcomes after TJR.

Overall, this study found that delirium is a common complication of TJR, occurring in approximately 17% of patients aged 50 years and over. This suggests that health care professionals who work with these patients should possess a sound understanding of the symptoms, course, risk factors, and management of delirium. As delirium may be associated with poorer post-surgical outcomes, a greater understanding of its development after TJR is required, with the view to developing and implementing preventative measures.

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Appendices

Search strategy for each data-base

Search period: January, 1980 - November, 2013

Pubmed.
(surgery[tw] OR surgical [tw] OR prosthe*[tw] OR endoprosthe* [tw]OR arthroplast*[tw] OR replacement[tw] OR procedure*[tw]) AND (hip[tw] OR knee[tw] OR joint[tw] OR orthopaedic[tw] OR orthopedic[tw] OR TJR [tw] OR THR[tw] OR TKR[tw] OR TJA[tw] OR THA[tw] OR TKA[tw]) AND (Delirium[mh] OR Confusion[mh] OR Delirium[tw] OR Confusion*[tw] OR Disorient*[tw])

PsycINFO.
(surgery.SH OR hips.SH OR knee.SH OR surgery.TI OR surgery.AB OR surgical.TI OR surgical.AB OR prosthe*.TI OR prosthe*.AB OR endoprosthe*.TI OR endoprosthe*.AB OR arthroplast*.TI OR arthroplast*.AB OR replacement.TI OR replacement.AB OR procedure*.TI OR procedure*.AB) AND (hip.TI OR hip.AB OR knee.TI OR knee.AB OR joint.TI OR joint.AB OR orthopaedic.TI OR orthopaedic.AB OR orthopedic.TI OR orthopedic.AB OR TJR.TI OR TJR.AB OR THR.TI OR THR.AB OR TKR.TI OR TKR.AB OR TJA.TI OR TJA.AB OR THA.TI OR THA.AB OR TKA.TI OR TKA.AB) AND (delirium.SH OR delirium.TI OR delirium.AB OR confusion*.TI OR confusion*.AB OR Disorient*.TI OR disorient*.AB)

Embase
('arthroplasty':de,ab,ti OR 'hip arthroplasty':de,ab,ti OR 'knee arthroplasty':de,ab,ti OR 'total knee replacement':de,ab,ti 'surgery':ab,ti OR 'surgical':ab,ti OR prosthe*:ab,ti OR endoprosthe*:ab,ti arthroplast*:ab,ti OR 'replacement':ab,ti OR procedure*:ab,ti) AND ('hip':ab,ti OR 'knee':ab,ti OR 'joint':ab,ti OR 'orthopedic':ab,ti OR 'orthopaedic':ab,ti OR 'TJR':ab,ti OR 'THR':ab,ti OR 'TKR':ab,ti OR 'THA':ab,ti OR 'TKA':ab,ti) AND ('delirium':de,ab,ti OR confusion*:ab,ti OR disorient*:ab,ti)

Scopus.
(surgery OR surgical OR prosthe* OR endoprosthe* OR arthroplast* OR replacement OR procedure*) AND (hip OR knee OR joint OR orthopaedic OR orthopedic OR TJR OR THR OR TKR OR TJA OR THA OR TKA) AND (Delirium OR Confusion* OR Disorient*)

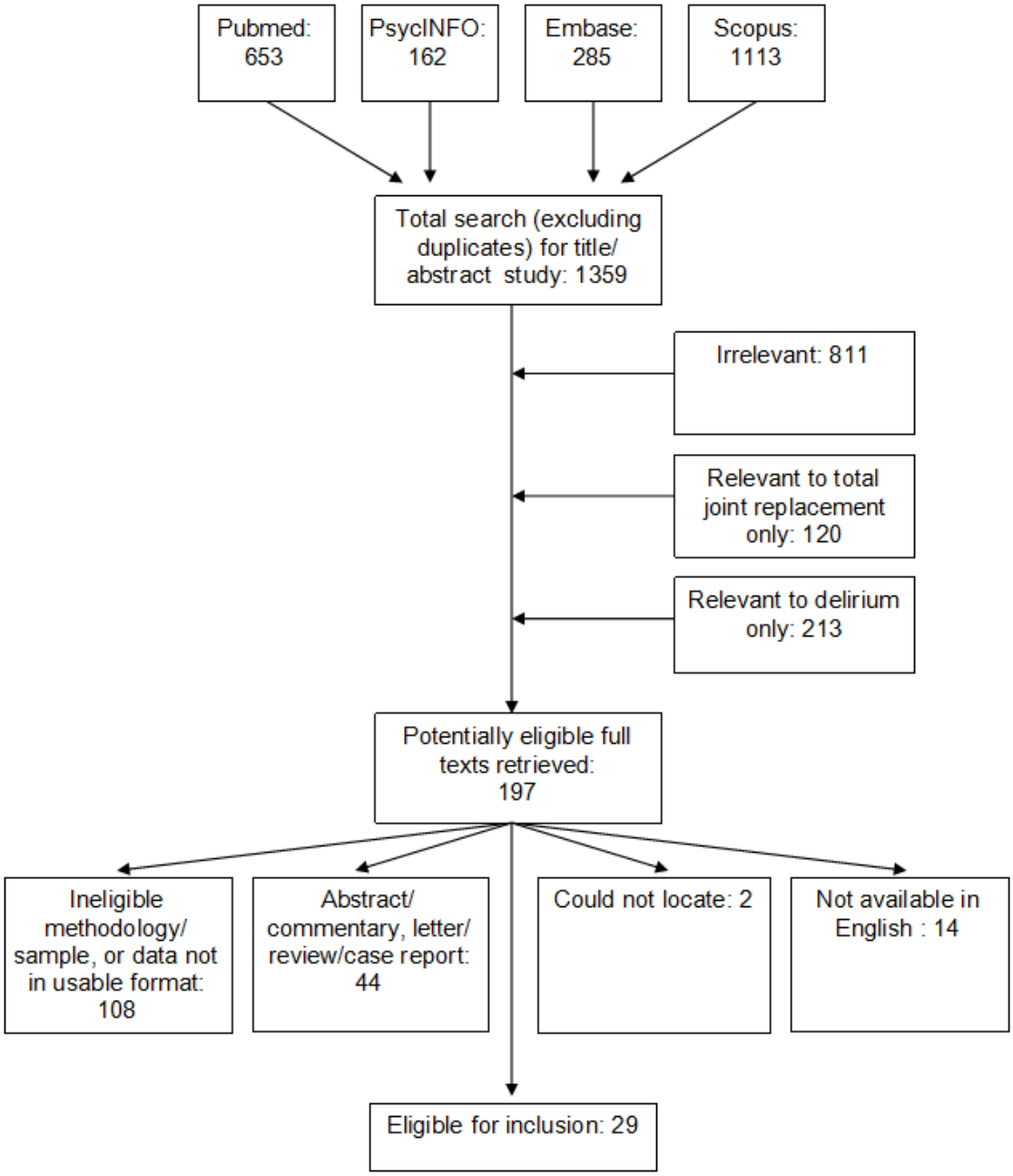

Figure 4-A: Outcomes of the database searches

Chapter 5. Study 3

Depression and anxiety after total joint replacement among older adults: A meta-analysis.

This chapter presents a published paper and the details of which are:

Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2016). Depression and anxiety after total joint replacement among older adults: a meta-analysis. *Aging and Mental Health, 20,* 1243-1242. doi:10.1080/13607863.2015.1072801

Statement of Authorship

Statement of Authorship

Title of Paper	Depression and anxiety after total joint replacement among older adults: a meta-analysis
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Scott, J. E., Mathias, J. L., & Kneebone, A. C. (2016). Depression and anxiety after total joint replacement among older adults: a meta-analysis. *Aging and Mental Health, 20*, 1243-1242. doi:10.1080/13607863.2015.1072801

Principal Author

Name of Principal Author (Candidate)	Julia Scott		
Contribution to the Paper	Conducted literature searches, coded articles, analysed and interpreted data, wrote manuscript.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Prof Jane Mathias		
Contribution to the Paper	Supervised and contributed to the study design, analysis and data interpretation, and manuscript preparation		
Signature		Date	25/11/16

Name of Co-Author	Dr Anthony Kneebone		
Contribution to the Paper	Assisted in evaluating and editing the manuscript		
Signature		Date	23/11/16

Please cut and paste additional co-author panels here as required.

Preface

As with research that has investigated cognitive outcomes, studies that have examined depression and anxiety in TJR patients have yielded mixed findings. It remains unclear how prevalent clinically significant levels of depression or anxiety are before and after surgery. The number of depression and anxiety symptoms has also been reported to increase, remain stable, and decrease post-surgery (See Chapter 1). As depression and anxiety are thought to have direct and indirect effects on recovery after TJR surgery, these outstanding questions regarding the prevalence and severity of depression and anxiety require clarification. Therefore, this final meta-analysis was designed to determine the incidence of clinically significant depression and anxiety in TJR patients pre- to post-surgery. In addition, this study examined the levels of, and degree of change in, depression and anxiety prior to surgery and at short, medium and long term intervals following surgery.

Abstract

Objective: Patients usually experience good physical recovery after Total joint replacement (TJR), however it is unclear whether mood also improves. The current meta-analysis examined changes in depression and anxiety following TJR in older (≥50 years) patients in order to address this gap in the literature.

Methods: Data from 26 studies (4,045 TJR, 55 controls) that assessed depression and/or anxiety pre- and post-surgery in TJR patients, with or without a control group, were analysed. Prevalence rates and Cohen's *d* effect sizes were used to evaluate changes in the prevalence and severity of depression/anxiety, respectively.

Results: Approximately 23% of TJR patients had clinically significant levels of depression prior to surgery, which decreased to 13% one year later. The prevalence of anxiety could not be evaluated due to the limited available data. TJR patients did not show any clinically meaningful reductions in symptoms of depression or anxiety, following surgery. Compared to controls, there was no difference in symptom progression over time; although only one study examined this.

Conclusions: TJR patients appear to have higher rates of clinically significant symptoms of depression before and after surgery, compared to the general population, however more research with adequate control groups is needed to confirm this. Only a modest improvement in the severity of depression and anxiety symptoms was noted post-surgery. However, existing research is limited; preventing definite conclusions regarding the impact of TJR on mood.

Total joint replacement (TJR) of the hip or knee is frequently performed on older adults to treat osteoarthritis (Harris & Sledge, 1990), with the number doubling over the past decade (Australian Orthopaedic Association National Joint Replacement Registry, 2012). TJRs are highly successful procedures, as they have low complication and revision rates (Labek, Thaler, Janda, Agreiter, & Stockl, 2011), and frequently provide significant improvements in pain and functionality (Harris & Sledge, 1990; Söderman, Malchau, & Herberts, 2000), with only a minority of patients experiencing ongoing problems (Beswick, Wylde, Gooberman-Hill, Blom, & Dieppe, 2012; Wylde & Blom, 2011). Given this success, it might be expected that TJR patients would also experience improvements in their symptoms of depression and anxiety, especially once their pain has subsided and physical function has begun to improve; however there is currently no consensus from the existing literature as to whether this occurs.

Ongoing symptoms of depression and anxiety after TJR surgery may negatively impact patients' post-surgical recovery. Specifically, TJR patients with higher levels of depression or anxiety have higher rates of post-surgical delirium (Kinjo, Lim, Sands, Bozic, & Leung, 2012) and 12-month mortality (Guerini, Morghen, Lucchi, Bellelli, & Trabucchi, 2010). They also report higher levels of medication-use (Singh & Lewallen, 2009); experience poorer functional improvement (Brander, Gondek, Martin, & Stulberg, 2007; Caracciolo & Giaquinto, 2005; Singh & Lewallen, 2009; Vissers et al., 2012); and require longer hospital admissions (Nickinson, Board, & Kay, 2009). Therefore, post-surgical symptoms of depression and anxiety may have wide-reaching impacts.

Various mechanisms have been proposed to explain the relationship between depression and mortality, albeit in cardiac surgery patients (Carney, Freedland, Miller, & Jaffe, 2002), which may also be applicable to TJR patients. One suggestion is that patients with higher levels of depression are less engaged in their rehabilitation, which

increases their risk of developing other health problems (Carney et al., 2002). Alternatively, depression may be a co-morbidity of other medical conditions, which are themselves risk factors for poorer outcome. For example, depressed persons have been found to have increased rates of hypertension and diabetes (Wells, Golding, & Burnam, 1989), which may independently affect their mobility and engagement in rehabilitation (Carney et al., 2002). Although the mechanism(s) remains unclear, depression appears to be a consistent and clinically-important predictor of poor outcome.

Estimates of the prevalence of depression and anxiety following TJR vary considerably, although high rates have generally been reported. Nickinson et al (2009), for example, found that 50% of TJR patients experienced clinically significant levels of depression symptoms 2- to 4-days after surgery, but only 5% remained so at discharge. Other studies have reported that approximately 15% to 24% of patients have clinically significant levels of depression in the year after their surgery (Riediger, Doering, & Krismer, 2010; Swinkels, Newman, & Allain, 2009). The rates of clinically significant levels of anxiety also vary, ranging from 8% to 85% (Montin et al., 2007; Wade, Riddle, & Thacker, 2012). This variability may, in part, be attributable to differences in the sample characteristics and timing of assessment. Specifically, some studies (Nickinson et al., 2009) excluded persons who experienced significant levels of anxiety prior to surgery and others (Montin et al., 2007; Riediger et al., 2010) did not. Moreover, post-surgical depression and anxiety have been assessed at different times, ranging from hospital discharge (Nickinson et al., 2009) to one year post-surgery (Montin et al., 2007; Riediger et al., 2010; Swinkels et al., 2009).

Although the rates of clinically significant levels of depression and anxiety following TJR vary, they are consistently higher than those seen in healthy older adults (2.5-6.5%; Mojtabai & Olfson, 2004; Trollor, Anderson, Sachdev, Brodaty, & Andrews, 2007); instead being more comparable to the rates seen in hospitalized older adults

(Koenig, George, Peterson, & Pieper, 1997) or patients undergoing cardiac and thoracic surgery (Andrew, Baker, Kneebone, & Knight, 2000; Kitagawa, Yasui-Furukori, Tsushima, Kaneko, & Fukuda, 2011; Krannich et al., 2007). Thus, despite the surgical success of the joint replacement, TJR patients appear to have an increased risk of clinically significant levels of depression and anxiety, compared to their healthy peers (Montin et al., 2007; Riediger et al., 2010; Swinkels et al., 2009).

One explanation for the higher prevalence of clinically significant levels of depression/anxiety following TJR is that these symptoms represent a normal response to surgery and illness-related stress (Newman, 1984), which would be expected to subside as patients recover. Prior to surgery, patients experience significant pain and disability, which may continue for several weeks post-surgery (Foran, 2011a, 2011b; Wells et al., 1989) and initially increase the risk of depression (Denkinger et al., 2014; Hawker et al., 2011). Furthermore, pain increases the risk of falls (Stubbs et al., 2014), with a fear of falling potentially causing additional anxiety (Hull, Kneebone, & Farquharson, 2013). Once the pain subsides, it would be expected that the symptoms of depression and/or anxiety may also reduce. However, this explanation has mixed support as levels of depression/anxiety have variously been reported to *reduce* (Duivenvoorden et al., 2013; Riediger et al., 2010; Vazquez, Staples, Sears, & Klodell, 2011), *remain stable* (Krannich et al., 2007; Montin et al., 2007; Pinna, Cremeans-Smith, Greene, & Delahanty, 2009; Swinkels et al., 2009), and *increase* (Andrew et al., 2000; Kitagawa et al., 2011) postoperatively in both TJR and cardio-thoracic patients of a similar age. Notably, however, those studies that reported a reduction in symptoms generally assessed either a broad age-range (28-81 years; Riediger et al., 2010) or a young sample (mean age=24.3 years; Vazquez et al., 2011), in contrast to those that reported no change or an increase in symptoms, which tended to assess older adults (Andrew et al., 2000; Montin et al., 2007; Pinna et al., 2009; Swinkels et al., 2009), or provided separate data for this subgroup (Krannich et al., 2007). Moreover, the latter

study found that symptoms decreased in younger patients, but were unchanged in the oldest group. Thus, older adults may be more susceptible to postoperative depression/anxiety.

Overall, the research suggests that a substantial proportion of older TJR patients suffer from clinically significant levels of depression and anxiety (Montin et al., 2007; Pinna et al., 2009; Riediger et al., 2010; Swinkels et al., 2009), which are linked to higher rates of mortality and morbidity (Guerini et al., 2010; Kinjo et al., 2012). However, the rates of clinically significant depression and anxiety in older TJR patients have yet to be thoroughly evaluated. The current study therefore undertook a quantitative meta-analysis of existing research that has examined levels of depression and anxiety in older adults following TJR.

Design and Methods

Search strategy

This meta-analysis was conducted as per the guidelines provided by the Meta-Analysis Reporting Standards (American Psychological Association, 2008). The PubMed, PsycINFO, Embase and Scopus data-bases were all searched to identify research - published between January 1980 and December 2014 - that assessed the symptoms of depression and/or anxiety after TJR (see Appendix A, on-line supplementary materials, for logic grids). To be included in this meta-analysis, a study needed to have: (1) examined patients who underwent standard elective TJR of the hip or knee (excludes experimental procedures); (2) recruited patients who were aged 50 years or older (when age range not provided: mean age minus 1 SD≥50 years); (3) used a standardized screening tool for depression and anxiety, such as the Beck Depression Inventory or the Geriatric Depression Scale (excludes single questions and generic ‘psychological distress’ subscales included in quality-of-life measures); (4)

conducted pre- and post-surgical assessments of either a single TJR sample or TJR and control samples; (5) reported data from which an effect size could be computed (proportions; means and SDs; *t*-test or exact probability values); (6) been published in a journal in English; and (7) a sample size greater than one (excludes case studies).

Studies were excluded if (1) they examined samples that were not broadly representative of the general TJR population (e.g. only married persons; Khan et al., 2009), (2) participants contributed multiple scores to the same data-set (e.g. if participants underwent more than one surgical procedure during the recruitment period and were assessed after each procedure (e.g. Jimenez, Zorrilla, Lopez-Alonso, Leon, & Salido, 2014)), or (3) some participants did not complete a pre-surgical assessment (i.e. missing baseline data; Mikkelsen, Petersen, Soballe, Mikkelsen, & Mechlenburg, 2014). Surgery was sometimes described as 'elective' hip/knee surgery, which includes partial or revision procedures, in addition to TJR. These samples were assumed to contain mostly TJR patients, and therefore included in this meta-analysis, because the majority of elective procedures involve total replacements (Australian Orthopaedic Association National Joint Replacement Registry, 2012).

Effect size calculation and analyses

The data extracted from the studies included within this meta-analysis were in the form of proportions or group means (and standard deviations). All analyses were calculated in Microsoft Excel, using the formulae provided by Lipsey and Wilson (2001). Proportions are an effect size and were used to indicate the prevalence of clinically significant levels of depression or anxiety following TJR, as determined by scores that fall above/below a designated cut-off for the particular depression/anxiety scale. Proportions obtained from individual studies underwent logit transformations, using the method recommended by Lipsey and Wilson (2001), before being combined to calculate a mean; after which they were transformed back to a proportion.

In addition, means (and SDs) were used to calculate Cohen's *d* effect sizes in order to quantify changes in the *levels* of depression/anxiety pre- and post-surgery. A variant of Cohen's *d* - d_{RM} - was calculated for the studies that used a single-sample (TJR) repeated-measures (pre- and post-surgery) design (Lipsey & Wilson, 2001). A negative d_{RM} indicates a decline in depression/anxiety symptoms pre- to post-surgery, while a positive d_{RM} suggests an increase in symptoms. An independent-groups repeated measures (pre- and post-surgery) Cohen's *d* (d_{IGRM}) (Morris & DeShon, 2002) was calculated for the single study that assessed TJR and healthy controls before and after surgery (Salazar et al., 2011). A negative d_{IGRM} indicates that the TJR patients experienced either a greater decrease or smaller increase in symptoms pre- to post-surgery, compared to controls over the same time period. A positive d_{IGRM}, on the other hand, indicates that TJR patients experienced a greater increase or smaller decrease in symptoms, compared to controls. The magnitude of d_{RM} and d_{IGRM} were judged according to the benchmarks suggested by Cohen (1988), with 0.2 indicating a 'small' effect (i.e change in symptoms), 0.5 a 'medium effect', and 0.8 a 'large' effect.

Larger samples yield more reliable estimates of the true population effect than smaller samples. Therefore, effects from individual studies were weighted by their inverse variance (i.e. inverse of the squared standard error; Lipsey & Wilson, 2001) before they were combined and averaged so that the findings from larger samples were weighted more heavily (Lipsey & Wilson, 2001). The inverse variance calculations for d_{RM} and d_{IGRM} both require the correlation (*r*) between the pre- and post-surgical assessments (Lipsey & Wilson, 2001; Morris & DeShon, 2002). However, no study reported these data; therefore a conservative estimated test-retest reliability of .7 was used, as this provided an acceptable compromise. A coefficient of .7 is considered to be the minimum acceptable reliability for published psychological tests (Gregory, 2011), consequently the current measures would be expected to meet this standard.

A random-effects model was used to analyse the data because of the heterogeneity between the individual effect sizes, established using the homogeneity test (based on the Q statistic) outlined in Lipsey and Wilson (2001). A random effects model assumes that individual effect sizes vary both due to sampling error and other unidentified sources of error (e.g. age of sample, level of pain), and factors these sources of error (sampling error, estimated random variance) into the standard error and inverse weight calculations (Lipsey & Wilson, 2001).

Ninety-five percent confidence intervals (95% CIs) and Fail-Safe *N* statistics (N_{fs}) were calculated for all effect sizes to assist with their interpretation. CIs provide a range of values within which the true population effect is likely to fall (Lipsey & Wilson, 2001), with an interval that includes zero indicating that the effect is not statistically significant. N_{fs} statistics were also calculated to take into account the tendency for journals to publish statistically significant results (Lipsey & Wilson, 2001). The N_{fs} statistic estimates the number of unpublished studies with non-significant findings that would be required to reduce a mean effect size to a level that would not be of clinical interest. For proportion data, this level was based on the mean 12-month prevalence for depression/anxiety in the older adult general population (≥ 50 years), as reported by the Australian Bureau of Statistics (depression/affective disorders = 4.0%; anxiety disorders = 9.8%; Australian Bureau of Statistics, 2009). For Cohen's *d*, this level was set as $d = .1$. The higher N_{fs} value, the less likely it is that publication bias would affect the current findings.

For present purposes, the results were considered indicative of noteworthy change in the levels of depression/anxiety symptoms following TJR, if the Cohen's *d* was moderate in size ($d \geq .5$ or $d \leq -.5$), statistically significant (95% CIs did not span zero), and the N_{fs} statistic was greater than $N_{studies}$.

Results

Search results

The literature search, which was kept broad in an effort to capture all relevant studies, initially identified 10,053 papers, excluding duplicates (refer to Figure A, online supplementary materials, for the flowchart). An initial review of the titles and abstracts reduced the number to 279, for which full-text versions were examined to establish eligibility. The main reasons for excluding full text articles are summarised in Figure A (supplementary materials).

A review of the full-texts revealed that some studies failed to provide all of the data needed to calculate an effect size, but met all other inclusion/exclusion criteria. If the study was published within the last decade (time-frame within which there was a reasonable likelihood that data would be available), the corresponding author was emailed with a request for the necessary data. To this end, the authors of twelve studies were contacted (Blackburn, Qureshi, Amirfeyz, & Bannister, 2011; Brander et al., 2007; Cremeans-Smith, Soehlen, Greene, Alexander, & Delahanty, 2009; Davis et al., 2009; Faller, Kirschner, & König, 2003; Harden et al., 2003; Inan et al., 2007; Salazar et al., 2011; Stecz & Kocur, 2014b; Swinkels et al., 2009; Utrillas-Compaired, De la Torre-Escuredo, Tebar-Martinez, & Asunsolo-Del Barco, 2014; Wade et al., 2012); seven of whom provided the requisite data (Cremeans-Smith et al., 2009; Davis et al., 2009; Faller et al., 2003; Salazar et al., 2011; Stecz & Kocur, 2014b; Swinkels et al., 2009; Utrillas-Compaired et al., 2014).

In total, 37 papers were deemed eligible for inclusion. An additional study (Stecz & Kocur, 2014a) was sent in response to a request for data and was subsequently included. Therefore a total of 38 studies were eligible for inclusion. It is a requirement of meta-analyses that all study samples are independent of one another in order to ensure that each sample only contributes once to the calculation of a mean

effect size (Lipsey & Wilson, 2001). Thus, all studies were checked to determine whether they examined independent samples; if independence could not be confirmed, studies were combined and treated as one. To this end, the data from (a) six sets of two studies by Badura-Brzoza et al. (Karina Badura-Brzoza et al., 2009; K. Badura-Brzoza et al., 2008), Orbell et al. (Orbell, Espley, Johnston, & Rowley, 1998; Orbell, Johnston, Rowley, Espley, & Davey, 1998), Davis et al. (Davis et al., 2009; Davis et al., 2011), Stecz & Kocur (Stecz & Kocur, 2014a, 2014b), Salazar et al. (Salazar et al., 2011; Salazar et al., 2014), and Swinkels et al. (Swinkels & Allain, 2013; Swinkels et al., 2009); (b) two sets of five studies by Pinto et al. (P. Pinto, McIntyre, Araujo-Soares, Ferro, & Almeida, 2014; P. R. Pinto, McIntyre, Araujo-Soares, Costa, & Almeida, 2014; P. R. Pinto, McIntyre, Ferrero, Almeida, & Araujo-Soares, 2013; P. R. Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013; P. R. Pinto, McIntyre, Ferrero, Araujo-Soares, & Almeida, 2013), and (c) one set of three studies by Creameans-Smith/Pinna et al. (Cremeans-Smith, Greene, & Delahanty, 2011; Cremeans-Smith, Soehlen, Greene, Alexander, & Delahanty, 2009; Pinna et al., 2009), were collapsed. Therefore, data from 26 independent studies were meta-analysed. Summary details for these individual studies (sample size; patient group: knee/hip/knee & hip; domain: depression/anxiety/both; measure; postoperative interval) are summarized in Table A of the online supplementary materials.

Research designs and data preparation

A total of 21 studies assessed depression or anxiety after TJR using a single-sample (TJR) repeated-measures design (pre- and post-surgery assessments; Attal et al., 2014; K. Badura-Brzoza et al., 2008; Cremeans-Smith et al., 2009; Dahlen, Zimmerman, & Barron, 2006; Davis et al., 2011; Duivenvoorden et al., 2013; Faller, Kirschner, & König, 2003; Hartley, Vance, Elliott, Cuckler, & Berry, 2008; Lopez-Olivio et al., 2011; McHugh, Campbell, & Luker, 2013; Montin et al., 2007; Orbell, Johnston, et al., 1998; Papakostidou et al., 2012; Patel, Stygall, Harrington, Newman, & Haddad,

2010; Perez-Prieto et al., 2014; P. R. Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013; Rodriguez et al., 2005; Smith & Zautra, 2004; Stecz & Kocur, 2014b; Swinkels et al., 2009; Utrillas-Compaired, De la Torre-Escuredo, Tebar-Martinez, & Asunsolo-Del Barco, 2014). An additional four studies involved clinical trials where patients were randomly allocated into 'treatment' (experimental) and 'standard care' groups that were assessed pre- and post-surgery (Buker et al., 2014; Lin, 2011; Pellino et al., 2005). For present purposes, only the 'standard care' data from these studies were analysed. Somewhat surprisingly, only one study (Salazar et al., 2011) used a control group to examine changes in depression and anxiety following TJR surgery (TJR & Control groups, assessed pre- and post-surgery), which meant that it could not be combined with any other study. The data for this single study were reported separately and the TJR group data were additionally analysed with that of the aforementioned 25 studies in order to maximize the available data.

The interval between surgery and the follow-up assessment varied substantially between studies, ranging from 24 hours to 12 months. Therefore, the studies were categorised into one of four broad intervals in order to ensure the data were broadly comparable: 'pre-discharge' (within one week of surgery), 'medium-term' (6- to 12-weeks post-surgery), 'six-months', and 'long-term' (9- to 12-months post-surgery). These categories accommodated most of the available data. However, data were excluded if a study performed more than one assessment within a single interval because each study can only contribute one effect size to the calculation of a mean effect (Lipsey & Wilson, 2001). When more than one assessment was conducted, the data for the interval that was most comparable to that used by the other studies within that same category were selected for analysis. Data were also excluded if the assessment period did not fall within one of these four intervals.

Participants

The 26 studies included in this meta-analysis assessed symptoms of depression and/or anxiety in a total of 4,045 TJR patients and 55 healthy controls (see Table 1). The majority of the TJR sample was female, and aged in their mid-60s to early-70s. In contrast, the controls consisted of equal numbers of males and females, and most were aged from their late-60s to early-80s. Too few studies provided comparable data relating to marital status ($N_{studies}$=7), education ($N_{studies}$=7), premorbid IQ ($N_{studies}$=1), or co-morbid medical conditions ($N_{studies}$=6) to reliably summarise. In addition, pain and physical function were inconsistently reported and therefore could not be summarised or considered within any analyses.

Nineteen studies assessed levels of depression ($N_{participants}$=3,624 TJR patients, $N_{participants}$=55 healthy controls) using the Hospital Anxiety and Depression Scale ($N_{studies}$=7), the Centre for Epidemiological Studies Depression Scale ($N_{studies}$=5), the Geriatric Depression Scale ($N_{studies}$=3), the Depression, Anxiety and Stress Scale ($N_{studies}$=1), the Beck Depression Inventory ($N_{studies}$=2), or the Mental Health Inventory ($N_{studies}$=1). Anxiety symptoms were assessed by 19 studies ($N_{participants}$=2,812 TJR patients, $N_{participants}$=55 healthy controls) using the Hospital Anxiety and Depression Scale ($N_{studies}$=10), the State-Trait Anxiety Inventory ($N_{studies}$=7), the Depression, Anxiety and Stress Scale ($N_{studies}$=1) or the Mental Health Inventory ($N_{studies}$=1).

Table 5-1: Summary demographic and surgery data for the total joint replacement and control groups

	TJR Group					Control Group				
	$N_{studies}$	$N_{participants}$	%	*M*	*SD*	$N_{studies}$	$N_{participants}$	%	*M*	*SD*
All studies										
Sample size	26	4045		155.6	209.5	1	55			
Age (years)	25	3935		68.0	3.9	1	55		74	6.3
Gender	26	4045								
Male			37.4			1	55	49.1		
Female			62.6			1	55	50.9		
Surgery Type	26	4045								
hip replacement	6		15.3							
knee replacement	13		47.0							
hip/knee replacement	7		37.7							
Assessed Depression	19	3624								
Assessed Anxiety	19	2812								

Note. TJR = total joint replacement, $N_{studies}$ = number of studies, $N_{participants}$ = number of participants.

Prevalence of clinically significant levels of depression and anxiety.

Six studies examined the prevalence of clinically significant levels of depression before TJR, four studies at 6-12 weeks and five studies at 6-12-months post-surgery (see Table 2). Approximately one in five patients had clinically significant levels of depression (scored above a cut-off) at baseline and three months post-surgery; however, this rate was substantially lower at 12 months. The N_{fs} were all high, indicating that these findings are unlikely to be affected by publication bias.

As seen in Table 2, six studies reported the prevalence of clinically significant levels of anxiety prior to surgery, one study at pre-discharge, and four studies at 6-12 weeks, and 6-12 months post-surgery. However, in the case of the 6-12 week and 6-12 month intervals, there was enormous variation in the rates reported by individual studies, with one reporting particularly high rates (Montin et al., 2007). Therefore, a mean prevalence rate could not be reliably calculated for these intervals.

Table 5-2: Prevalence of depression and anxiety in total joint replacement patients

	$N_{studies}$	$N_{participants}$	*Range (%)*	P_M	*95% CI*		N_{fs}	*References*
Depression								
Pre-surgery	6	1442	5.7- 37.1	22.9	12.5	38.1	29	(Duivenvoorden et al., 2013; Faller et al., 2003; Perez-Prieto et al., 2014; Pinna et al., 2009; Swinkels et al., 2009; Utrillas-Compaired et al., 2014)
6-12 week follow-up	4	714	10.8 - 35.4	22.2	11.8	37.6	18	(Duivenvoorden et al., 2013; Faller et al., 2003; Pinna et al., 2009; Swinkels et al., 2009)
12 month follow-up	5	1344	1.0 - 30.5	12.7	5.0	28.4	11	(Duivenvoorden et al., 2013; Faller et al., 2003; Perez-Prieto et al., 2014; Swinkels et al., 2009; Utrillas-Compaired et al., 2014)
Anxiety								
Pre-surgery*	6	451	15.7 - 85.0					(Dahlen et al., 2006; Duivenvoorden et al., 2013; Faller et al., 2003; Montin et al., 2007; Stecz & Kocur, 2014b; Utrillas-Compaired et al., 2014)
Pre-discharge*	1	23	8.7					(Dahlen et al., 2006)
6-12 week follow-up*	4	477	10.5 - 95.3					(Duivenvoorden et al., 2013; Faller et al., 2003; Montin et al., 2007; Stecz & Kocur, 2014b)
6- 12 month follow-up*	4	617	11.2 - 94.2					(Duivenvoorden et al., 2013; Faller et al., 2003; Montin et al., 2007; Utrillas-Compaired et al., 2014)

Note. CIs are uneven as a function of a logit–to-proportion transformation
$N_{studies}$=number of studies, $N_{participants}$=number of participants, P_M=weighted mean prevalence, 95% CI=95% confidence intervals, N_{fs}=Fail safe N
**P_M, 95% CIs and N_{fs} not calculated due to the low number of available studies and large variability within the data.*

Changes on the severity of depression and anxiety symptoms pre- to post-surgery

Nineteen studies assessed changes in levels of depression in TJR samples pre- and post-surgery, with most focusing on symptoms at 6-12 weeks, 6-months, or 9-12 months (see Table 3). Small, but statistically significant, negative effects were observed from 6-12 weeks onwards, indicating that the number or severity of depressive symptoms decreased. Although the N_{fs} statistics indicate that these are robust findings, the size of these effects suggest that these changes are not clinically meaningful.

As indicated, only one study (Salazar et al., 2011) used a control group to examine changes in symptoms of depression following TJR (see Table 3). This study assessed symptoms of depression pre-surgery, pre-discharge and 12-weeks post-surgery using the Hospital Anxiety and Depression Scale. There was a small but significant negative effect pre-discharge, with acceptable N_{fs}, indicating that the TJR group showed a greater decrease in levels of depression after surgery than the controls over an equivalent period. However, this effect was small and would not, therefore, equate to noteworthy change. A closer examination of the data revealed that, despite experiencing a small but significant decrease in symptoms prior to their hospital discharge, TJR patients experienced higher levels of depression than their peers both *before* undergoing surgery (*d*=.46) and 12-weeks *after* their surgery (*d*=.24).

Nineteen studies assessed the level of anxiety symptoms in a TJR sample, with six to nine studies examining each interval. As seen in Table 4, there were small to low-moderate, but significant reductions in the levels of anxiety at the 6-12 week, 6-month, and 9-12 month intervals, compared to baseline; however these reductions did

not meet the study criteria for meaningful or noticeable changes in mood, although the effect size at 9-12 months came close.

Table 5-3: Change in symptoms of depression before and after total joint replacement

TJR pre- and post-surgery data

Follow-up interval	$N_{studies}$	$N_{participants}$	d_{RM}	*95% CI*		N_{fs}	*Study references*
Pre-discharge (3-7 days)	2	92	-.14	-.48	.19	1	(Rodriguez et al., 2005; Salazar et al., 2011)
Medium-term (6-12 weeks)	11	1707	-.24*	-.31	-.18	15	(Buker et al., 2014; Cremeans-Smith et al., 2009; Davis et al., 2011; Duivenvoorden et al., 2013; Faller et al., 2003; Hartley et al., 2008; Orbell, Johnston, et al., 1998; Patel et al., 2010; Rodriguez et al., 2005; Salazar et al., 2011; Swinkels et al., 2009)
Six months	9	1769	-.22*	-.34	-.10	11	(Attal et al., 2014; K. Badura-Brzoza et al., 2008; Buker et al., 2014; Davis et al., 2011; Lopez-Olivio et al., 2011; McHugh et al., 2013; Patel et al., 2010; Smith & Zautra, 2004; Swinkels et al., 2009)
Long-term (9-12 months)	10	1983	-.31*	-.40	-.23	21	(Attal et al., 2014; Buker et al., 2014; Davis et al., 2011; Duivenvoorden et al., 2013; Faller et al., 2003; McHugh et al., 2013; Orbell, Johnston, et al., 1998; Papakostidou et al., 2012; Swinkels et al., 2009; Utrillas-Compaired et al., 2014)

TJR and Control pre- and post-surgery data

Follow-up interval	$N_{studies}$	$N_{participants}$	d_{IGRM}	*95% CI*		N_{fs}	*Study references*
Pre-discharge (4 days)	1	129	-.27*	-.47	-.07	2	(Salazar et al., 2011)
Medium-term (12 weeks)	1	118	-.19	-.39	-.01	1	(Salazar et al., 2011)

$N_{studies}$=number of studies, $N_{participants}$=number of participants, d_{RM}=weighted mean single-sample repeated measures Cohen's d, d_{IGRM}=weighted mean independent-groups repeated measures Cohen's d, 95% CI=95% confidence intervals, N_{fs}=fail-safe N
**satisfies criteria for statistically significant change ($d \geq .2$, CI ≠ 0, $N_{fs} < N_{studies}$)*

Table 5-4: Change in symptoms of anxiety before and after total joint replacement

TJR pre- and post-surgery

Follow-up interval	$N_{studies}$	$N_{participants}$	d_{RM}	*95% CI*		N_{fs}	*Study References*
Pre-discharge (1-4 days)	6	336	-.34	-.69	.02	14	(Dahlen et al., 2006; Giraudet-Le Quintrec et al., 2003; Lin, 2011; Pellino et al., 2005; P. R. Pinto, McIntyre, Ferrero, Almeida, & Araújo-Soares, 2013; Salazar et al., 2011)
Medium-term (6-12 weeks)	9	1527	-.38*	-.59	-.16	25	(Dahlen et al., 2006; Davis et al., 2011; Duivenvoorden et al., 2013; Faller et al., 2003; Montin et al., 2007; Orbell, Espley, et al., 1998; Patel et al., 2010; Salazar et al., 2011; Stecz & Kocur, 2014b)
Six-month	8	1722	-.11	-.25	.02	8	(Attal et al., 2014; K. Badura-Brzoza et al., 2008; Davis et al., 2011; Lopez-Olivio et al., 2011; McHugh et al., 2013; Montin et al., 2007; Patel et al., 2010; Smith & Zautra, 2004)
Long-term (9-12 months	7	1666	-.47*	-.56	-.38	26	(Attal et al., 2014; Davis et al., 2011; Duivenvoorden et al., 2013; Faller et al., 2003; McHugh et al., 2013; Orbell, Espley, et al., 1998; Utrillas-Compaired et al., 2014)

TJR and Control pre- and post-surgery

Follow-up interval	$N_{studies}$	$N_{participants}$	d_{IGRM}	*95% CI*		N_{fs}	*Study References*
Pre-discharge (4 days)	1	129	.11	-.07	.29	0	(Salazar et al., 2011)
Medium-term (12 weeks)	1	118	-.04	-.24	.16	0	(Salazar et al., 2011)

$N_{studies}$=number of studies, $N_{participants}$=number of participants, d_{RM} =weighted mean single-sample repeated measures Cohen's d, d_{IGRM}=weighted mean independent-groups repeated measures Cohen's d, 95% CI=95% confidence intervals, N_{fs}=fail-safe N
**satisfies criteria for significant change ($d \geq .2$, CI ≠ 0, $N_{fs} < N_{studies}$)*

Finally, the one study (Salazar et al., 2011) that assessed anxiety in TJR and Control groups found small but non-significant group differences in the changes to levels of anxiety from baseline to pre-discharge and 12-weeks post-surgery (see Table 4). However, the mean anxiety levels of the TJR patients were significantly higher than those of the healthy controls at the pre-surgical (*d*=.35), pre-discharge (*d*=.40), and 12-week (*d*=.24) assessments. Thus, while TJR patients and controls had comparable changes in levels of anxiety over time, TJR patients were more anxious at each interval, although this difference was lowest at the time of the final assessment.

Discussion

This meta-analysis investigated post-surgical depression and anxiety in older TJR patients (N_{TJR}=4,045). Approximately one in five people reported experiencing clinically significant levels of depression prior to and three-months after TJR surgery, which decreased to a rate of one-in-eight 12 months after surgery. However, the latter finding appears to have been affected by the very low prevalence rate from a single large-scale study (*N*=716; Perez-Prieto et al., 2014). When excluded, the prevalence rate was 21 (95% CI=12.6-33.3), which was comparable to the pre-surgical and 12-week post-surgical rates. These rates are all higher than those generally observed in older adults, although less so at 12-months when the Pérez-Prieto et al. data are included (Australian Bureau of Statistics, 2009). However, the lack of control data limits our ability to draw any firm conclusions about the comparability of these rates to those of healthy older adults. The rates of clinically significant levels of depression in TJR patients are comparable to those seen in cardiac surgery patients (Ravven, Bader, Azar, & Rudolph, 2013), but are lower than those of thoracic surgery (Kitagawa et al., 2011; Okamoto, Motomura, Murashima, & Takamoto, 2013) and hip fracture (Guerini et al., 2010; Phillips, Upton, Duggal, Carroll, & Lord, 2013).

The six studies that examined the prevalence of clinically significant levels of anxiety symptoms reported rates that ranged between 9% and 95%. Of these, four (Faller et al., 2003; Montin et al., 2007; Stecz & Kocur, 2014b; Utrillas-Compaired et al., 2014) reported post-surgical rates that were much higher than those seen in the general population (Australian Bureau of Statistics, 2009), while the remainder (Dahlen et al., 2006; Duivenvoorden et al., 2013) reported a marginally higher pre-surgical, but comparable post-surgical, rate. The substantial variation in rates of clinically significant symptoms of anxiety between studies may, in part, be explained by the measures that were used. Four studies (Dahlen et al., 2006; Duivenvoorden et al., 2013; Faller et al., 2003; Utrillas-Compaired et al., 2014) used the Hospital Depression and Anxiety Scale, while two studies (Montin et al., 2007; Stecz & Kocur, 2014b) used the State-Trait Anxiety Scale, one of which reported very high rates (above 85%; Montin et al., 2007). It has been proposed that the cut-off scores used within the latter study may be too low for use among older adults (Julian, 2011). In contrast, the cut-off scores used by Stecz and Kocur (2014b) were slightly higher and adjusted for both age and sex. When Montin et al. (2007) was excluded, the mean baseline rate was 48, at 6-12 weeks it was 25, and at 6-12 months it was 23. However, given the small number of studies included in these calculations, these results should be interpreted with caution.

An analysis of the severity of depression and anxiety symptoms following TJR revealed moderate improvements up to 12 months post-surgery. Ultimately, these improvements in the number or severity of symptoms may not reflect observable changes with real-world impact. Unfortunately, only one relatively small study used a healthy older control group (N_{TJR}=63, $N_{controls}$=55) to assess depression and anxiety symptoms in TJR patients. This study found that TJR patients showed fewer symptoms of depression prior to their discharge, compared to controls; however, this difference was small and unlikely to reflect meaningful change. Importantly, TJR patients had higher levels of depression both prior to and 12 weeks after their surgery,

highlighting the importance of including a control group to evaluate surgical outcomes. With regard to symptoms of anxiety, although TJR patients and healthy controls did not differ in terms of change over time, the patients had higher levels of anxiety at each assessment.

Overall, the findings suggest that TJR is associated with a modest improvement in the levels of depression and anxiety over time, although it is unclear whether this was uniform across all persons. If symptoms of depression and anxiety were closely linked to pain (Denkinger et al., 2014) and physical function (Hull et al., 2013), then a greater improvement may have been expected at long term follow-up. Therefore, it is possible that the symptoms of depression and anxiety increased in some patients, while other patients improved or remained the same. Although it would be clinically useful to identify these subgroups, this requires data for individuals showing their change pre- to post-surgery, and these data were rarely reported. Similarly, although the prevalence of clinically significant cases of depression remained relatively constant in the first year after surgery, it is not clear whether they are the same or different people. These results indicate that group and individual data should be provided in order to accurately evaluate the impact of TJR on symptoms of depression and anxiety.

There are some limitations to this meta-analysis that warrant noting. First, only one study used a control group, making it difficult to assess whether TJR patients experience higher levels of depression/anxiety than the general population (Morris & DeShon, 2002). Second, there was no differentiation between patients with situational versus chronic symptoms, as these subgroups may respond differently to an event like TJR. Third, a small percentage of the patients may have undergone revision total replacement because eleven studies failed to specify whether their inclusion criteria extended to revision TJR. Conceivably, revision patients may have different psychological outcomes because they have prior experience of what is to follow.

Although the exact number of revision patients is not known, it is likely that they were very limited in number because the majority of TJRs are first-time procedures (Australian Orthopaedic Association National Joint Replacement Registry, 2014). Fourth, a number of studies assessed depression and anxiety using measures that are not well-suited to elderly persons with physical illnesses. Specifically, two of the five measures (Centre for Epidemiological Studies Depression Scale, Depression and Anxiety Stress Scales) assess neuro-vegetative symptoms (e.g., changes in sleep, loss of energy), which are affected by normal ageing and illness; potentially inflating the resulting depression/anxiety scores. Moreover, a reduction in levels of depression/anxiety after surgery may reflect physical recovery (e.g. sleep may improve due to reduced pain), rather than an improvement in mood. To test this notion, studies that assessed depression within the 6-12 week interval were divided into two groups: one that used a measure that included neuro-vegetative symptoms ($N_{studies}$=5) and one that did not ($N_{studies}$=6). Although a comparison of the mean depression scores of the two groups failed to find a significant difference here (*d*=-.22, CI=-.34, -.10 vs *d*=-.26, CI=-.34, -.19), the potential confounding effect of physical comorbidities should be considered when assessing depression (Olin, Schneider, Eaton, Zemansky, & Pollock, 1992). Furthermore, concerns have been raised regarding the use of these scales with patients who have cognitive impairments (Burke, Houston, Boust, & Roccaforte, 1989). As many studies did not report excluding such patients, it is likely that a minority of patients had some form of cognitive impairment, which may undermine the validity of their results. In addition, it should be noted that scores above the cut-offs on these scales do not equate to a diagnosis of a mood disorder (e.g. Major Depressive Disorder), which rely on thorough clinical interview (Mitchell, Vaze, & Rao, 2009).

Fourth, although comprehensive, this meta-analysis may have missed some studies that examined depression/anxiety, but failed to mention this in the title, abstract or key words, or where these variables were incidental to the main purpose of the

study. Fifth, some studies had to be excluded because they assessed patients who fell below the current age criteria (mean age minus 1 SD≥50 years) or did not provide adequate data to determine whether the sample met the inclusion criteria (Nickinson et al., 2009; Riediger et al., 2010). Given the typical demographic characteristics of TJR patients (Australian Orthopaedic Association National Joint Replacement Registry, 2012), it is possible that some of these studies may have been eligible, had they provided more information. Sixth, some of the studies reported small sample sizes (e.g. *N*=23; Dahlen et al., 2006). While accepted weighting methods were used (Lipsey & Wilson, 2001), the results from these studies may not be as generalizable to the broader TJR population. Finally, it was necessary to exclude an additional five studies because they did not provide all of the data needed to calculate an effect size and this data could not be obtained from the authors (Blackburn, Qureshi, Amirfeyz, & Bannister, 2011; Brander et al., 2007; Harden et al., 2003; Inan et al., 2007; Wade et al., 2012).

Critically, this meta-analysis highlights the need for high-quality research that (1) includes a demographically-matched control group, (2) uses standardised measures of depression and/or anxiety that are appropriate for use with elderly samples who may have physical illnesses (i.e., do not assess the somatic aspects of depression/anxiety), (3) reports both group and individual data, and (4) provides data for other variables that may be related to depression and anxiety (e.g., pain, functional recovery, co-morbid medical conditions). A control group is required to determine whether TJR patients experience higher levels of depression and anxiety than their healthy peers. Scales that are specifically designed for older adults, such as the Hospital Anxiety and Depression Scale or the Geriatric Depression Scale, should be used to provide a more reliable assessment of mood in this older medically-compromised group. Group data should be reported in order to monitor changes in the prevalence and levels of depression, and individual data is needed to evaluate both

change, and whether there is a subgroup of patients who have better/worse outcomes than the group as a whole. Lastly, data for variables – especially pain, functional recovery and comorbid conditions - should need to be provided in a consistent manner using more comparable measures so their relationship with postoperative depression and anxiety can be examined.

In conclusion, approximately one in five TJR patients experience clinically significant levels of depression prior to, and up to six-months after, their surgery. This rate appears to decrease one-year after surgery, although this finding may have been inflated by results of one particular study. The specific prevalence of clinically significant levels of anxiety among TJR patients remains unclear, because very few studies have reported these data and their results vary considerably. Unfortunately, due to a lack of control data, it cannot be confirmed how these rates compare to that of healthy older adults. As a group, TJR patients do not appear to experience a clinically meaningful decrease in their levels of depression or anxiety in the first year after their surgery, compared to their pre-surgery levels. The findings from one study, which compared the depression and anxiety symptoms of TJR patients to their healthy peers, suggest that TJR patients generally experience more symptoms, but there were either no group differences, or only small or group differences in the change of symptoms over time. Given the limited availability of good-quality research, it is difficult to decisively evaluate the impact of TJR on mood. Furthermore, it was not possible to investigate the potential moderating influence of pain, functionality or medical comorbidities on symptoms of depression and anxiety. Considering the poor outcomes that are associated with depression and anxiety in TJR patients, in conjunction with the potential for intervention (e.g. Cooney et al., 2013) this gap in the literature needs to be addressed as a matter of urgency.

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Appendices

Appendix A

Search Strategies for each data-base

Search period: January, 1980 - December, 2014

Pubmed.

(surgery[tw] OR surgical[tw] OR prosthe*[tw] OR endoprosthe* OR arthroplast*[tw] OR replacement[tw] OR procedure*[tw]) AND (hip[tw] OR knee[tw] OR joint[tw] OR orthopaedic[tw] OR orthopedic[tw] OR TJR [tw] OR THR[tw] OR TKR[tw] OR TJA[tw] OR THA[tw] OR TKA[tw]) AND (Affect[mh] OR Depression[mh] OR Depressive disorder[mh] OR Mental disorders[mh:noexp] OR Anxiety[mh] OR Anxiety Disorders[mh] OR Mood*[tw] OR Affective[tw] OR Depressi*[tw] OR Mental disorder*[tw] OR Anxi*[tw] OR Nervousness[tw] OR Psychiatric diagnosis[tw] OR Emotional state*[tw] OR Emotional stress[tw] OR Fear[tw] OR Psychological[tw] OR Melancholi*[tw] OR Mental illness[tw] OR Psychiatric disorder*[tw] OR Psychopathol*[tw] OR Dysthymi*[tw] OR Distress[tw] OR Anguish[tw] OR Sadness[tw] OR Angst[tw] OR Worr*[tw] OR Apprehension[tw] OR Neurosis[tw] OR Psychoneurosis[tw] OR Abnormal psycholog*[tw] OR Cothymia[tw] OR Emotion disorder[tw] OR Emotional disturbance[tw])

PsycINFO.

(surgery.SH OR hips.SH OR knee.SH OR surgery.TI OR surgery.AB OR surgical.TI OR surgical.AB OR prosthe*.TI OR prosthe*.AB OR endoprosthe*.TI OR endoprosthe*.AB OR arthroplast*.TI OR arthroplast*.AB OR replacement.TI OR replacement.AB OR procedure*.TI OR procedure*.AB) AND (hip.TI OR hip.AB OR knee.TI OR knee.AB OR joint.TI OR joint.AB OR orthopaedic.TI OR orthopaedic.AB OR orthopedic.TI OR orthopedic.AB OR TJR.TI OR TJR.AB OR THR.TI OR THR.AB OR TKR.TI OR TKR.AB OR TJA.TI OR TJA.AB OR THA.TI OR THA.AB OR TKA.TI OR TKA.AB) AND (Affective Disorders.SH OR Major Depression.SH OR Emotional States.SH OR Mental Disorders.SH OR Psychopathology.SH OR Distress.SH OR Depression.SH OR Abnormal Psychology.SH OR Sadness.SH OR Psychiatric symptoms.SH OR Major Depression.SH Or Dysthymic Disorder.SH OR Reactive depression.SH OR Anxiety Disorders.SH OR Anxiety.SH OR Fear.SH OR Neurosis.SH OR abnormal psycholog*.TI OR abnormal psycholog*.AB OR Mental disorder*.TI OR Mental disorder*.AB OR Mental illness.TI OR Mental illness.AB OR psychiatric disorder*.TI OR psychiatric disorder*.AB OR emotional state*.TI OR emotional state*.AB OR psychopathol*.TI OR psychopathol*.AB OR Affective.TI OR Affective.AB OR Mood*.TI OR Mood*.AB OR Depressi*.TI OR Depressi*.AB OR Dysthymi*.TI OR Dysthymi*.AB OR Melancholi*.TI OR Melancholi*.AB OR distress.TI OR distress.AB OR anguish.TI OR Anguish.AB OR sadness.TI OR sadness.AB OR anxi*.TI OR anxi*.AB OR angst.TI OR angst.AB OR worry.TI OR worry.AB OR apprehension.TI OR apprehension.AB OR fear.TI OR fear.AB OR neurosis.TI OR neurosis.AB OR psychoneurosis.TI OR psychoneurosis.AB OR cothymia.TI OR cothymia.AB

Embase.

('arthroplasty':de,ab,ti OR 'hip arthroplasty':de,ab,ti OR 'knee arthroplasty':de,ab,ti OR 'total knee replacement':de,ab,ti 'surgery':ab,ti OR 'prosthe*':ab,ti OR 'endoprosthe*':ab,ti OR 'surgical':ab,ti OR arthroplast*:ab,ti OR 'replacement':ab,ti OR procedure*:ab,ti) AND ('hip':ab,ti OR 'knee':ab,ti OR 'joint':ab,ti OR 'orthopedic':ab,ti OR 'orthopaedic':ab,ti OR 'TJR':ab,ti OR 'THR':ab,ti OR 'TKR':ab,ti OR 'THA':ab,ti OR 'TKA':ab,ti) AND ('mood disorder':de,ab,ti OR 'mood disturbance':ab,ti OR 'mood disturbances':ab,ti OR 'affective neurosis':de,ab,ti OR

‘emotional disorder’:de,ab,ti OR ‘major affective disorder’:de,ab,ti OR ‘minor affective disorder’:de,ab,ti OR ‘postoperative depression’:de,ab,ti OR ‘depression’:de,ab,ti OR ‘dysthymia’:de,ab,ti OR ‘melancholia’:de,ab,ti OR ‘mixed anxiety and depression’:de,ab,ti OR ‘long term depression’:de,ab,ti OR ‘anxiety’:de,ab,ti OR ‘fear’:de,ab,ti OR ‘anxiety disorder’:de,ab,ti OR ‘anticipatory anxiety’:de,ab,ti OR ‘emotional stress’:de,ab,ti OR ‘affective’:ab,ti OR depress*:ab,ti OR ‘mood’:ab,ti OR ‘mental illness’:ab,ti OR ‘mental disorder’:ab,ti OR ‘mental disorders’:ab,ti OR psychologic*:ab,ti OR dysthymi*:ab,ti OR ‘cothymia’:ab,ti OR ‘emotion disorder’:ab,ti OR ‘emotional disturbance’:ab,ti OR Anxi*:ab,ti OR ‘Abnormal psychology’:ab,ti OR psycholog*:ab,ti OR psychopathol*:ab,ti OR ‘distress’:ab,ti OR ‘anguish’:ab,ti OR ‘sadness’:ab,ti OR ‘angst’:ab,ti OR ‘worry’:ab,ti OR ‘apprehension’:ab,ti OR ‘fear’:ab,ti OR ‘neurosis’:ab,ti OR ‘psychoneurosis’:ab,ti)

Scopus.

**Search limited to journal articles, articles-in-press and English*

(surgery OR prosthe* OR endoprosthe* OR surgical OR arthroplast* OR replacement OR procedure*) AND (hip OR knee OR joint OR orthopaedic OR orthopedic OR TJR OR THR OR TKR OR TJA OR THA OR TKA)AND(Affect OR Depression OR “Depressive disorder” OR “Mental disorders” OR Anxiety OR “Anxiety Disorders” OR Mood* OR Affective OR Depressi* OR “Mental disorder*” OR Anxi* OR Nervousness OR “Psychiatric diagnosis” OR “Emotional state*” OR “Emotional stress” OR Fear OR Psychological OR Melancholi* OR “Mental illness” OR “Psychiatric disorder*” OR Psychopathol* OR Dysthymi* OR Distress OR Anguish OR Sadness OR Angst OR Worr* OR Apprehension OR Neurosis OR Psychoneurosis OR “Abnormal psycholog*” OR Cothymia OR “Emotion disorder*” OR “Emotional disturbance*”)

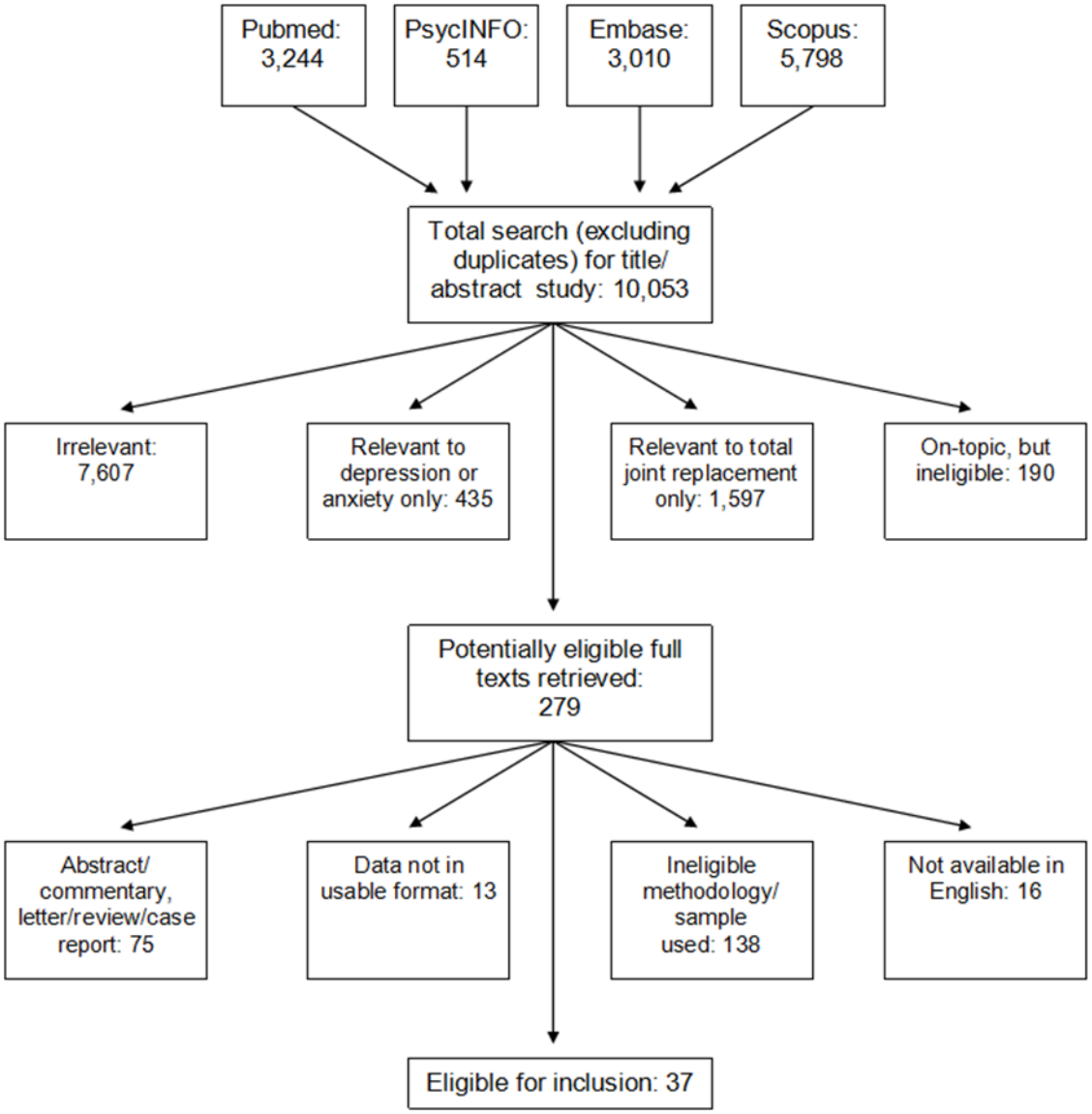

Figure 5-A: Flow chart detailing the outcomes of the database searches, and application of the inclusion/exclusion criteria

Table 5-A: Individual study characteristics

Study	$N_{participants}$	Patient type	Domain assessed	Measure used	Postoperative assessment	Data provided
Attal et al. (2014)	89	Total knee replacement	Depression/Anxiety	Beck Depression Inventory/ State-Trait Anxiety Inventory (State Anx)	6 months, 12 months	M (SD)
Badura-Brzoza et al. (2008)/ Badura-Brzoza et al. (2009)	184	Total hip replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	6 months	M (SD)
Buker et al. (2014)	34	Total knee replacement	Depression	Beck Depression Inventory	3 months, 6 months, 12 months	M (SD)
Cremeans-Smith et al. (2011)/ Cremeans-Smith et al. (2009)/ Pinna et al. (2009)	Up to 110	Total knee replacement	Depression	Centre for the Epidemiologic Studies Depression Scale	3 months	M (SD), %
Dahlen et al. (2006)	23	Total knee replacement	Anxiety	Hospital Anxiety and Depression Scale	3 days, 3 months	M (SD), %
Davis et al. (2009)/ Davis et al. (2011)	924	Total hip/knee replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	3 months, 6 months, 12 months	M (SD)
Duivenvoorden et al. (2013)	268	Total hip/knee replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	3 months, 12 months	M (SD), %
Faller et al. (2003)	60	Total knee replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	3 months, 12 months	M (SD), %
Giraudet-Le Quintrec et al. (2003)	52	Total hip replacement	Anxiety	State-Trait Anxiety Inventory (State Anx)	7 days	M (SD)
Hartley et al. (2008)	62	Partial/total hip/knee replacement	Depression	Centre for the Epidemiologic Studies Depression Scale	6 weeks	M (SD)
Lin (2011)	48	Total hip/knee replacement	Anxiety	State-Trait Anxiety Inventory	3 days	M (SD)
Lopez-Olivio et al. (2011)	241	Knee replacement	Depression/ Anxiety	Depression, Anxiety and Stress Scale	6 months	M (SD)
McHugh et al. (2013)	181	Total hip replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	6 months, 12 months	M (SD)
Montin et al. (2007)	87	Primary/revision Total hip replacement	Anxiety	State-Trait Anxiety Inventory (State Anx)	3 months, 6 months	M (SD), %
Orbell, Johnston et al. (1998)/ Orbell, Espley et al. (1998)	72	Total hip/knee replacement	Depression/ Anxiety	Centre for the Epidemiologic Studies Depression Scale/	3 months, 9 months	M (SD)

				Hospital Anxiety and Depression Scale		
Papakostidou et al. (2012)	184	Total knee replacement	Depression	Centre for the Epidemiologic Studies Depression Scale (short form)	12 months	M (SD)
Patel et al. (2010)	45	Total hip replacement	Depression/ Anxiety	Centre for the Epidemiologic Studies Depression Scale / State-Trait Anxiety Inventory (State Anx)	6 weeks, 6 months	M (SD)
Pellino et al. (2005)	32	Total hip/knee replacement	Anxiety	State-Trait Anxiety Inventory (State Anx)	3 days	M (SD)
Perez-Prieto et al. (2014)	716	Total knee replacement	Depression	Geriatric Depression Scale (short form)	12 months	%
Pinto, McIntyre, Ferrero, Almeida, Araujo-Soares (2013)a/ Pinto, McIntyre, Ferrero, Almeida, Araujo-Soares (2013)b/ Pinto, McIntyre, Ferrero, Araujo-Soares et al. (2013)/ Pinto, McIntyre, Araujo-Soares, Ferro, Almeida (2014)/ Pinto, McIntyre, Araujo-Soares, Costa, Almeida (2014)	124	Total hip/knee replacement	Anxiety	Hospital Anxiety and Depression Scale	2 days	M (SD)
Rodriguez et al. (2005)	28	Total knee replacement	Depression	Geriatric Depression Scale	7 days, 3 months	M (SD)
Salazar et al. (2011)/ Salazar et al. (2014)	63	Total knee replacement\ Healthy controls	Depression/ Anxiety	Hospital Anxiety and Depression Scale	4 days, 3 months	M (SD)
Smith & Zautra	64	Total Knee replacement	Depression/ Anxiety	Mental Health Inventory	6 months	M (SD)
Stecz & Kocur (2014)a/ Stecz & Kocur (2014)b	61	Total hip replacement	Anxiety	State-Trait Anxiety Inventory (State Anx)*	3 months	M (SD), %
Swinkels & Allain (2009)/ Swinkels et al. (2009)	99	Total knee replacement	Depression	Geriatric Depression Scale	3 months, 6 months, 12 months	M (SD), %
Utrillas-Compared et al. (2014)	202	Total knee replacement	Depression/ Anxiety	Hospital Anxiety and Depression Scale	12 months	M (SD), %

*Polish standardization cut-off points used for prevalence data

Chapter 6. Study 4

Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients.

This chapter presents a published paper the details of which are:

Scott, J. E., Mathias, J. L., Kneebone, A. C., & Krishnan, J. (2016). Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients. *Journal of Clinical and Experimental Neuropsychology, In Press*.

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Statement of Authorship

Statement of Authorship

Title of Paper	Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients.
Publication Status	☑ Published ☑ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Scott, J. E., Mathias, J. L., Kneebone, A. C., & Krishnan, J. (2016). Postoperative cognitive dysfunction and its relationship to cognitive reserve in elderly total joint replacement patients. *Journal of Clinical and Experimental Neuropsychology, In Press.* doi:10.1080/13803395.2016.1233940

Principal Author

Name of Principal Author (Candidate)	Julia Scott		
Contribution to the Paper	Study inception, design, methodology (including participant assessments, data entry literature searches, statistical analysis and data interpretation), and wrote manuscript		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Preface

Study 1 (Chapter 3) evaluated the literature that has examined POCD after TJR. Unfortunately, this study could not reach any firm conclusions regarding the incidence or severity of POCD after TJR for several reasons. First, the studies did not use comparable definitions of POCD, therefore the incidence of POCD could not be meaningfully aggregated across studies. Furthermore, the studies tended to rely on group data (i.e. means and SDs), which may fail to detect a decline in a subgroup of patients, especially when practice effects are not controlled for (Newman, 1995). Finally, only two studies used a control group, therefore it was not possible to disentangle genuine cognitive change from the effects of repeated testing, such as practice effects (Slade, Sanchez, Townes, & Aldea, 2001).

Ultimately, this meta-analysis revealed that a well-designed and statistically rigorous clinical study was needed to investigate whether patients experience POCD following TJR. More specifically, it identified the need for a control group. However, there has been some debate as to whether a surgical control or healthy control group should be used when assessing the cognitive functioning of surgical samples (Murkin, Newman, Stump, & Blumenthal, 1995; Newman, 1995; Slade et al., 2001). A surgical control group would be required to determine whether TJR, as opposed to other types of surgery, is uniquely related to POCD. Such a group controls for the effects of surgery (Newman, 1995), including anaesthesia and analgesia, pain, admission to hospital and the stresses associated with surgery (Slade et al., 2001). The utility of a surgical control group depends on their comparability to the TJR group and therefore it would need to be equivalent in terms of demographics (i.e. age, gender and education), pre- and postoperative pain, functional disability and analgesic use. It

would also need to be similar with respect to surgical details, such as anaesthetic (type and time under anaesthetic), invasiveness and complexity of the surgical procedure, length of hospital admission, and recovery time. Consequently, it is difficult to find a surgical control group that is sufficiently comparable to a TJR patient group in all these areas (Newman, 1995).

A second option would be to use a healthy control group, which controls for the confounds that arise with repeated testing (Kneebone, Andrew, Baker, & Knight, 1998; Newman, 1995). Importantly, healthy controls should be as comparable as possible to the TJR group in terms of demographics, education, health, and baseline cognitive function in order to provide an adequate comparison for TJR patients once they have recovered from surgery. A healthy control group is the comparison group recommended for the assessment of cognitive function after surgery, but it must be recognised that such a group cannot control for the effects of surgery (Murkin et al., 1995; Newman, 1995; Slade et al., 2001).

Another problem with the existing literature was that it did not provide individual change data, which are needed to identify those patients who experienced significant cognitive decline after TJR (Newman, 1995). Furthermore, 'impairment' needs to be defined in a theoretically and statistically meaningful way. Therefore, standardised regression-based methodology (SRB; Sawrie, Chelune, Naugle, & Lüders, 1996) was used to measure cognitive change pre- to post-surgery because it controls for practice effects, regression to the mean, and measurement error, in addition to other factors that may affect retest performance, such as age, estimated premorbid IQ, gender, or retest-interval length. The SRB method uses test-retest data from a healthy control group to generate a 'predicted' postoperative cognitive score on all tests for each patient. Participants' predicted and actual retest scores are compared, and in the absence of POCD, it is expected that these scores will be similar. If the difference between the predicted and actual scores fall outside the 90% confidence interval, this

change is considered to be statistically rare and indicative of significant cognitive change. Therefore, the SRB method provides a statistically defensible means by which impaired cognitive performance can be identified and is more likely to provide a reliable estimate of POCD after TJR than other statistical criteria (Sawrie et al., 1996). Group data from patients and controls were also provided to provide a comparison to previous research that commonly presented results this way.

SRB methodology has not yet been used in the literature that has examined POCD following TJR. Although it could be argued that the use of the SRB method adds to the problem of inconsistent definitions of POCD, the benefits of this method (uses a control group, controls for repeated testing confounds, provides a statistically defensible POCD definition) were thought to outweigh this disadvantage. Furthermore, as it has been argued that this method is likely to provide the most accurate measurement of POCD (Sawrie et al., 1996), it is hoped that it will be used more consistently in future research examining POCD.

The clinical study presented in the following chapter used a battery of cognitive tests to assess different aspects of cognition. As POCD can impact different cognitive domains, it is important that a range of abilities are assessed (Murkin et al., 1995). In addition, these tests were chosen because they were thought to be sensitive to subtle or mild cognitive dysfunction (American Psychiatric Association, 2013). Arguably, studies that used cognitive batteries (Evered et al., 2011; Gray, Torrens, Howie, Christie, & Robinson, 2008; Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011), as opposed to brief cognitive screens, may provide a more accurate assessment of POCD following TJR. The tests were selected to cover a wide range of cognitive domains, according to the recommendations made by the Statement of Consensus on Assessment of Neurobehavioural Outcomes after Cardiac Surgery (Murkin et al., 1995), and to be comparable to previous studies.

Lastly, this clinical study assessed long-term POCD (six months), whereas many studies assessed cognitive dysfunction far earlier (e.g. prior to hospital discharge). It is recommended that the assessment of POCD involves at least one assessment at least three months post-surgery when patient's cognitive state is likely to be more stable (Murkin et al., 1995). Existing research (Chapter 3) has found preliminary evidence of cognitive decline pre-discharge. However, no conclusions could be drawn with regard to long-term POCD, leaving this question unanswered.

This study also assessed a number of other variables that are potentially relevant to the development of POCD, including surgical details (anaesthesia, implant type), demographics (age, education), comorbid conditions and current medication use, pre-morbid IQ, pain, quality of life, and depression and anxiety. Moreover, it used an independent groups (TJR patient, healthy control) pre- post-surgery design to investigate POCD after TJR.

The primary aim of this study was to assess the incidence and severity of POCD after TJR using SRB methodology and a cognitive battery. The second aim was to determine whether cognitive reserve predicted the development of POCD after TJR, which has not yet been examined (See Chapter 2). Few studies have been able to assess cognitive function and cognitive reserve prior to injury, which is possible using an elective TJR sample. Ropacki et al (2007) also achieved this using assessed elective cardio thoracic bypass graft surgery patients (Ropacki, Bert, Ropacki, Rogers, & Stern, 2007), and the current study endeavored to build on their findings in several ways. First, this study used the Cognitive Reserve Index Questionnaire, which measures multiple domains of cognitive reserve in a standardised and reliable manner (Nucci, Mapelli, & Mondini, 2011). Second, it used a control group and SRB methodology, providing a more rigorous assessment of cognitive change. Lastly, it looked at long-term POCD, whereas Ropacki et al. assessed patients within one week of CABG surgery.

Abstract

Introduction: Whether total joint replacement (TJR) patients are susceptible to postoperative cognitive dysfunction (POCD) remains unclear due to inconsistencies in research methodologies. Moreover, cognitive reserve may moderate the development of POCD after TJR, but has not been investigated in this context. The current study investigated POCD after TJR, and its relationship with cognitive reserve, using a more rigorous methodology than has previously been utilised.

Method: Fifty three older adults (aged 50+) scheduled for TJR were assessed pre- and post-surgery (six months). Forty five healthy controls matched for age, gender and premorbid IQ were re-assessed after an equivalent interval. Cognition, cognitive reserve, and physical and mental health were all measured. Standardised regression-based methods were used to assess cognitive changes, while controlling for the confounding effect of repeated cognitive testing.

Results: TJR patients only demonstrated a significant decline in Trail Making Test part B (TMT B) performance, compared to controls, and cognitive reserve only predicted change in TMT B scores among a subset of TJR patients. Specifically, patients who showed the most improvement pre to post-surgery had significantly higher reserve than those who showed the greatest decline.

Conclusions: The current study provides limited evidence of POCD after TJR when examined using a rigorous methodology, which controlled for practice effects. Cognitive reserve only predicted performance within a subset of the TJR sample. However, the role of reserve in more cognitively compromised patients remains to be determined.

Total joint replacement (TJR) of the hip or knee is increasingly used to treat severe osteoarthritis in older adults, with the demand for these procedures increasing dramatically in recent years (Australian Orthopaedic Association National Joint Replacement Registery, 2015). TJR is generally considered to be a highly successful procedure because the majority of patients experience substantial relief from both the pain and functional disability caused by their arthritis (Wylde & Blom, 2011). However some patients reportedly develop cognitive problems post-surgery (Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011). Known as postoperative cognitive dysfunction (POCD), this decline in cognitive performance can affect a variety of domains, including memory, information processing and executive functioning (Deiner & Silverstein, 2009). Typically, these deficits are subtle and may not be evident until months after surgery, when a patient has returned to their everyday activities (Krenk & Rasmussen, 2011). POCD is important because it is associated with a poorer quality of life (Funder, Steinmetz, & Rasmussen, 2009) and an increased risk of mortality, work cessation and placement in a nursing home (Steinmetz, Christensen, Lund, Lohse, & Rasmussen, 2009).

It is not yet known what causes POCD following TJR surgery. General anaesthesia – which has direct pharmacological effects on the brain (Williams-Russo, Sharrock, Mattis, Szatrowski, & Charlson, 1995) – may increase the risk of POCD, but this explanation has not been supported (Ancelin et al., 2010; Williams-Russo et al., 1995). Alternatively, postoperative analgesia has been investigated as a potential contributor to POCD (Zywiel, Prabhu, Perruccio, & Gandhi, 2013), however a systematic review of elderly surgical patients failed to find a relationship (Fong, Sands, & Leung, 2006). Postoperative pain has also been investigated as a possible cause of POCD. Poor pain management has been associated with cognitive decline soon after surgery (Duggleby & Lander, 1994), but is less likely to cause POCD in the longer term (3-6 months), by which most TJR patients have significantly reduced pain levels (Holt,

2015). Lastly, cerebral microemboli – caused by fat or marrow may entering the blood during surgery – may lead to POCD after TJR, with microemboli being reported in 23% to 100% of hip (Edmonds, Barbut, Hager, & Sharrock, 2000; Gray, Torrens, Howie, Christie, & Robinson, 2008; Koch et al., 2007; Patel, Stygall, Harrington, Newman, & Haddad, 2010; Riding et al., 2004) and 38% to 100% of knee (Kalairajah, Cossey, Verrall, Ludbrook, & Spriggins, 2006; Koch et al., 2007; Riding et al., 2004; Rodriguez et al., 2005; Sulek, Davies, Enneking, Gearen, & Lobato, 1999) replacements. However, a link between microemboli and POCD has not yet been established in TJR samples (Gray et al., 2008; Koch et al., 2007; Rodriguez et al., 2005) or in cardiac patients (Kruis, Vlasveld, & Van Dijk, 2010).

Research examining the presence and severity of POCD following TJR has been also hampered by a number of methodological problems. Although some studies indicate that TJR patients are vulnerable to POCD (Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011), a recent meta-analysis was unable to determine the frequency or severity of POCD in the long term (Scott, Mathias, & Kneebone, 2014). This was, in part, due to the fact that researchers used inconsistent definitions of POCD, including a decline of two or more standard deviations on two or more cognitive measures (Salazar et al., 2011) and a decrease of half a standard deviation or more on at least three cognitive tests (Deo, West, Butcher, & Lewis, 2011); leading to substantial variation in the incidence of POCD after TJR (Scott et al., 2014). Second, the potentially confounding effects of repeated cognitive testing (S.M. Sawrie, Chelune, Naugle, & Lüders, 1996) – which include practice effects, measurement error and regression to the mean – have not been taken into consideration; which means that it is not possible to determine whether TJR surgery affects cognition (Scott et al., 2014). These issues can be addressed by including a matched control group (Kneebone, Andrew, Baker, & Knight, 1998; S.M. Sawrie et al., 1996) and by using standardised regression-based methodology, which controls for the aforementioned confounds by

estimating their impact on follow-up cognitive performance. However, to date, control groups have rarely been incorporated in studies of POCD following TJR and standardised regression has not been used to define the extent and frequency of postoperative cognitive change (Scott et al., 2014).

A rigorous examination of POCD following TJR additionally provides the opportunity to investigate potential predictors of POCD, with cognitive reserve being one such variable. Cognitive reserve refers to the protective effect attributed to a person's (pre-surgical) cognitive abilities and compensatory strategies (Robertson, 2014; Watson & Joyce, 2015). Cognitive reserve is typically assessed using proxy measures that are thought to reflect these cognitive abilities, such as education level, occupational attainment, and the pursuit of cognitively stimulating leisure activities (Liberati, Raffone, & Belardinelli, 2012; Stern, 2009). It has been suggested that people with greater cognitive capacity, flexibility, and compensatory abilities are better able to cope with brain pathology (Robertson, 2014; Stern, 2009). For example, greater cognitive reserve is associated with better cognitive outcomes in persons with neurological disorders, such as multiple sclerosis (Benedict, Morrow, Weinstock Guttman, Cookfair, & Schretlen, 2010; Sumowski et al., 2013) and dementia (Lane, Paul, Moser, Fletcher, & Cohen, 2011; Murray et al., 2011; Valenzuela, 2008), and following heart failure (Alosco et al., 2012). Notably, TJR patients with greater cognitive reserve have been shown to have a lower risk of postoperative delirium (Tow & Verghese, 2013). However, the relationship between cognitive reserve and POCD following TJR has not been investigated. Conceivably, cognitive reserve may moderate the relationship between embolic load and POCD, possibly helping to explain why previous studies have failed to find a direct relationship between the two.

The current study therefore examined whether TJR patients are susceptible to POCD by assessing a TJR surgical and matched control group pre- and post-surgery (equivalent interval for controls), using standardised regression-based methodology to

control for practice effects, regression to the mean and measurement error. This methodology defines POCD as a significant statistically rare decline in an individual's performance, thereby providing an empirically-based and defensible definition of cognitive decline. Cognitive reserve was also examined as a potential predictor of POCD after TJR in order to determine whether it plays a protective role.

Methods

Participants

Participants were recruited from patients who were wait-listed for elective unilateral total hip or knee replacement at the Repatriation General Hospital, Adelaide, South Australia (January-November, 2013). Eligible persons were 50 years or older, fluent in English, free of neurocognitive disorders (determined by hospital staff from case notes), and had not undergone surgery within the last six months. The maximum number of patients were recruited during the study period.

Of the 67 TJR patients assessed pre-surgery, 53 completed the six-month follow-up assessment. Patients lost to follow-up included three whose surgery was cancelled or delayed beyond the recruitment period, four declined to continue, one could not be contacted, two moved interstate, one suffered a stroke, and three underwent further surgery prior to follow-up (débridement of infected prosthesis, second TJR, elective back surgery).

Patients were admitted to hospital on the day of surgery, and TJR was performed under general or regional anaesthesia, or a combination of both. Surgeons chose the type of anaesthetic, in consultation with the anaesthetist and patient. Surgery took approximately 1.5 hours and patients were mobilised within 24 hours and began physiotherapy one day post-surgery. In the absence of complications (e.g., nausea, wound ooze), TJR patients were discharged from hospital three to five days

after surgery. Patients were typically prescribed paracetamol, codeine, and/or oxycontin to manage pain when discharged, and were expected to have made a full recovery by six to twelve months post-surgery.

Selection criteria were the same for healthy controls, who were matched to the TJR sample for age, gender, marital status and estimated premorbid IQ. Controls were either friends/family members of the TJR patients (n=15, 31%) or were recruited from the general community via community groups and word-of-mouth (n=33, 69%). A total of 48 controls were initially recruited and assessed at baseline, 45 of whom completed the six-month follow-up assessment. One control participant declined to continue, a second was excluded after undergoing a general anaesthetic between the two assessments, and a third was being investigated for suspected mild cognitive impairment.

Procedure

This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee and the University of Adelaide Human Research Ethics Committee. Participants were assessed by the first author (JES) on two occasions (baseline, six-month follow-up), in a quiet room either at the Repatriation General Hospital or in the participants' homes. For TJR patients, baseline assessment occurred within the three weeks before surgery, with the exception of one patient whose surgery was delayed for five weeks due to a mild viral infection (Range: 2-48 days, M=8.8, SD=7.1, Median=7). Demographic, medical history, and pain data were collected, and the cognitive battery and all questionnaires were completed during the baseline assessment, which took between 1.5 and 2 hours.

Participants underwent a follow-up assessment approximately six months after TJR surgery, or an equivalent interval for controls (refer to Table 2); by which time they would have experienced significant physical recovery, ceased taking strong

analgesics, and cognition should have stabilised (Murkin et al., 1995). Demographic, comorbidity medication and pain details were updated and the cognitive battery, Short Form (36) Health Survey Version 2, and Hospital Depression and Anxiety Scale were re-administered. Follow-up assessments took 1 to 1.5 hours to complete.

Measures

Demographic information, including age, sex, ethnicity, marital status and socio-economic status (Australian Bureau of Statistics, 2014) was collected from all participants at baseline. Multiple surgical/medical details were recorded, including the length of hospital admission (days), anaesthetic type (regional, general or combination), implant type (cemented, uncemented, hybrid), complications, and medications (name, dosage, length of time taken). Measures of physical and psychological wellbeing were administered to participants at each assessment (see Table 1 for details). Lastly, cognitive reserve was assessed at baseline using the Cognitive Reserve Index Questionnaire (Nucci, Mapelli, & Mondini, 2011), which provides three sub-scores (based on respondents' education, occupation and engagement in cognitively stimulating leisure activities over their adult life), in addition to a 'total' cognitive reserve score. All scores are weighted by age and standardised to have a mean of 100 (SD=15). This questionnaire has been shown to provide a reliable measure of cognitive reserve, although concurrent validity remains difficult to establish in the absence of a 'gold standard' measure of cognitive reserve (Nucci et al., 2011).

A battery of cognitive tests was selected to assess POCD to ensure that the measures used would be sufficiently sensitive to detect subtle cognitive decline. Cognitive tests were selected on the basis of previous research (Scott et al., 2014) and the recommendations contained within the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery (Murkin, Newman, Stump, & Blumenthal, 1995). A broad range of cognitive domains was assessed including motor

and information processing speed, selective attention, learning and memory, executive functioning and estimated (premorbid) IQ. Cognitive Reserve was also measured. Details of the tests and scoring methods are provided in Table 1.

Table 6-1: Summary of details of the cognitive, physical, and psychological measures

Cognitive Measures		
Domain	*Test*	*Outcome measure*
Speed		
Motor Speed	*Purdue Pegboard (Tiffin & Asher, 1948)*	*No. of pegs placed, average of both hands (max. score 25)*
	Trail Making Test A (Reiten, 1992)	*Seconds to completion*
Processing speed	*Symbol-Digit Modalities Task (Smith, 1995)*	*Total substitutions in 90 secs (max. score 110)*
Selective Attention	*Letter Cancellation Task (Wilson, Cockburn, & Halligan, 1988)*	*Total errors (max. score 30)*
Memory	*Rey Auditory Verbal Learning Test (RAVLT) (Schmidt, 1996)*	
Learning	*RAVLT Trial 1 - 5*	*Total words recalled Trial 1-5 (max. score 75)*
Delayed recall	*RAVLT 30 minute delay*	*Total words recalled (max. score 15)*
Executive Function		
Verbal fluency	*FAS Initial Letter Fluency (Tombaugh, Kozak, & Rees, 1999)*	*Total score across three trials*
Inhibition	*Color-Word Interference Test Trial 3 (Delis, Kaplan, & Kramer, 2001)*	*Seconds to completion/proportion of items correct (Townsend & Ashby, 1983)*
Switching	*Color-Word Interference Test Trial 4 (Delis et al., 2001)*	*Seconds to completion/proportion of items correct (Townsend & Ashby, 1983)*
Mental flexibility	*Trail Making Test B (Reiten, 1992)*	*Seconds to completion*
IQ estimation	*Test of Premorbid Function (Pearson, 2009)*	*Predicted full scale IQ (M=100, SD=15)*
Cognitive Reserve	*Cognitive Reserve Index Questionnaire (Nucci, Mapelli & Mondini, 2011)*	*Total and subscale (education, occupation, leisure activities) scores. (M=100, SD=15). Higher scores indicate greater cognitive reserve*
Physical health and psychological well-being measures		
Physical Health	*Test*	*Outcome measure*
Pain	*Visual Analogue Scale 'How much pain are you currently experiencing?' (Portenoy & M., 1996)*	*Scores range from 0-100. 0 = 'no pain'; 100 = 'worst pain imaginable.'*
	SF-36 v2 Bodily Pain Subscale (Ware, 2000)	*Scores range from 0-100 (M=50, SD=10). Higher scores represent greater pain*
Mortality Risk	*Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987)*	*Higher score represents greater 10-year mortality risk*
Quality of Life (Physical Health)	*SF-36 v2 Physical Component Summary (Ware, 2000)*	*Scores range from 0-100 (M=50, SD=10). Higher scores represent greater quality of life*
Psychological Wellbeing	*Test*	*Outcome measure*
Depression	*Hospital Depression and Anxiety Scale (Zigmond & Snaith, 1983)*	*Scores range from 0-21, ≥ 8 indicate clinically significant distress (Bjelland, Dahl, Haug, & Neckelmann, 2002)*
Anxiety	*Hospital Depression and Anxiety Scale (Zigmond & Snaith, 1983)*	*Scores range from 0-21, ≥ 8 indicate clinically significant distress (Bjelland et al., 2002)*
Quality of Life (Mental Health)	*SF-36 v2 Mental Component Summary (Ware, 2000)*	*Scores range from 0-100 (M=50, SD=10). Higher scores represent greater quality of life*

Note: SF-36 v2 = Short Form (36) Health Survey, Version 2; RAVLT = Rey Auditory Verbal Learning Test, CW Interference = Color-Word Interference

Statistical Analysis

The TJR and Control groups were initially compared using t-tests, chi-square analyses and effect sizes (means & SDs: Cohen's d; proportions: phi) to ensure the two groups were matched at baseline on the demographic and cognitive measures. Cohen's d effect sizes of d=.2, d=.5, d=.7 and d= 2.0 indicate small, medium, large and very large effect sizes, respectively (Burke, Mathias, & Denson, 2015; Cohen, 1988). Phi effect sizes of phi=.1, phi=.3, and phi=.5 indicate a small, medium and large effect sizes, respectively (Pallant, 2005).

Standardized regression-based (SRB) methodology (S.M. Sawrie et al., 1996) was used to assess the changes in cognitive performance from baseline to follow-up, while controlling for practice effects, regression to the mean, and measurement error. The 6-month follow-up cognitive scores of control participants were regressed against their baseline scores and other variables that may influence follow-up performance (age, gender, IQ estimation, follow-up interval) in order to provide a 'predicted' follow-up score for individual patients on each cognitive test. The following equation was used: $Yp=C+B1(X1)\ldots+Bk(Xk)$, where Yp represents the predicted follow-up score, C is the constant, B1 is the regression coefficient for the baseline score, X1 is the actual baseline score, and Bk and Xk are the regression coefficients and actual values for the other variables (age, gender, IQ estimation, follow-up interval) that enter the regression. The difference between patients' predicted and actual follow-up scores was then converted into z-scores (SRB change scores) using the formula: $z = (Yo–Yp)/SEest$, where Yo represents the actual follow-up score, Yp the predicted follow-up score, and SEest the standard error of the regression equation estimate. A negative z-score indicates that a person's actual follow-up score fell below their predicted score, a positive z-score indicates they performed better than predicted, and a z-score of 0 indicates no difference between the obtained and predicted scores. All z-scores that fell above 1.64 or below -1.64 (90% confidence intervals) were deemed to indicate

statistically uncommon improvement or decline, respectively. It was expected that, by chance, 5% of healthy controls would fall into each of these categories. Chi-square test were used to compare the incidence of decline in TJR patients and controls on each measure. Mean z-scores for patients and controls were also calculated to compare the overall distribution of scores in each group.

Lastly, linear and nonlinear relationships between POCD and cognitive reserve were investigated using Pearson's r correlations, and quadratic and cubic regressions. Independent groups t-tests, accompanied by Cohen's d effect sizes were used to determine whether the levels of cognitive reserve observed in the TJR and Control groups were comparable.

Results

Participant details

The final TJR sample consisted of 53 patients, all of whom had a primary diagnosis of osteoarthritis. Twenty-nine TJR patients underwent a total hip replacement and 24 had total knee replacements. The majority of patients had hybrid prostheses (combination of cemented and uncemented components) and underwent regional anaesthesia. The average length of admission was five days (refer to Table 2). No major complications were reported in this sample during their hospital admission or the six-month follow-up interval.

Participants in both groups (TJR patients, Controls) were aged in their 60s to 70s, with slightly more females than males, and most being married (see Table 2). Although the TJR group had completed significantly fewer years of education, and lower levels of cognitive reserve compared to controls, the IQ estimates were comparable, suggesting that both groups were well-matched intellectually. TJR patients also had a lower mean socioeconomic level compared to controls. Separate

analyses were conducted to address these differences between the TJR patient and control group. In terms of physical health, the TJR patient group took more medications at baseline than controls and reported greater pain (large effects; d=.74, d=-2.30 respectively), which was not unexpected given their diagnosis of osteoarthritis underpinning their surgery, but had a comparable risk of mortality (Charlson Comorbidity Index). Not surprisingly, TJR patients' scores on the Physical Component Scale of the Short Form (36) Health Survey (SF-36) were significantly lower than that of controls at baseline, indicating that they were much more functionally impaired (very large effect; d=-3.00). In contrast, TJR patients Mental Component Scale scores were comparable to those of controls. However, the TJR group reported significantly more symptoms of depression and anxiety (moderate to large effects; d=.85, d=.51). There was also a trend for TJR patients to have a higher rate of clinically significant levels of anxiety symptoms (scored ≥8 on the Hospital Depression and Anxiety Scale) compared to controls, but this difference was not significant. Importantly, despite baseline differences in years of education, cognitive reserve, and symptoms of depression and anxiety, TJR patients and controls performed comparably on all of the cognitive measures at baseline (refer to Table 2).

To check for response bias the baseline demographic, health, and cognitive data of the TJR sample (N=53) were compared with the baseline data for the 14 patients who were lost to follow-up. These analyses showed that the final TJR sample were older (large effect, d=.76), experienced more pain and reported fewer symptoms of anxiety (moderate effects; d=.43, d=-.62, respectively), but were comparable to those lost to follow-up on all cognitive tests (See Table A, Supplementary Materials). Therefore, it is unlikely that the differences between the sample that completed this study and those who were lost to follow-up would impact substantially on the current findings.

Table 6-2: Baseline total joint replacement and healthy control group characteristics

	Baseline						Six-Month Follow-up					
	TJR Patients (N = 53)		Healthy Controls (N = 45)				TJR Patients (N = 53)		Healthy Controls (N = 45)			
	M	*SD*	*M*	*SD*	*p*	*d*	*M*	*SD*	*M*	*SD*	*p*	*d*
Surgical details												
Length of Admission	5.0	2.6										
	N	*%*										
Total Hip replacement	29	54.7										
Total Knee replacement	24	45.3										
Prosthesis type												
Cemented	14	26.4										
Uncemented	10	18.9										
Hybrid	29	54.7										
Anaesthetic Type												
General anaesthesia	4	7.6										
Regional anaesthesia	36	67.9										
Combination general/regional	13	24.5										
Demographic & background	*M*	*SD*	*M*	*SD*	*p*	*d*	*M*	*SD*	*M*	*SD*	*p*	*d*
Age	70.0	7.2	68.1	7.1	.185	.27						
Assessment Interval (days)	197.2	11.1	201.4	16.0	.135	-.31						
Years of Education	11.1	2.9	12.7	3.8	.022	-.47						
Estimated IQ	106.0	9.9	108.6	10.3	.204	-.26						
CRIQ (total)	113.4	14.1	121.0	12.6	.006	-.57						
SES Decile (1-10)	5.3	2.5	6.9	2.5	.003	-.64						
Charlson Comorbidity Index	3.9	1.1	3.7	1.1	.324	.17						
Number of medications	4.5	3.0	2.5	2.4	.001	.74	4.1	3.2	2.6	2.3	.007	.54
Bodily Pain subscale (SF-36)	30.20	15.6	72.3	20.9	.000	-2.30	59.9	23.2	75.6	21.8	.001	-.70
SF 36 PCS	31.7	6.3	50.5	6.2	.000	-3.00	42.2	9.3	50.4	7.2	.000	-.99
SF 36 MCS	51.7	10.8	54.1	7.0	.209	-.26	56.2	9.1	56.2	6.2	.984	.00
HADS depression	4.6	3.2	2.3	2.1	.000	.85	3.2	2.6	2.1	1.6	.015	.51
HADS anxiety	6.5	3.6	4.8	3.0	.014	.51	4.1	2.9	4.2	3.1	.934	-.03

Table 6-2: Baseline total joint replacement and healthy control group characteristic cont.

	Baseline						Six-Month Follow-up					
	TJR Patients (N = 53)		Healthy Controls (N = 45)				TJR Patients (N = 53)		Healthy Controls (N = 45)			
	N	*%*	*N*	*%*	*p*	*phi*	*N*	*%*	*N*	*%*	*p*	*phi*
Female	31	58.5	*24*	53.3	.685	.05						
Married/Defacto	*35*	*66.0*	*38*	*84.4*	.062	-.21						
HADS depression (% ≥ 8)	8	15.7	2	4.4	.098	.18	5	9.6	0	0	.063	.21
HADS anxiety (% ≥ 8)	18	35.3	8	17.8	.067	.20	5	9.6	5	11.9	.748	-.04
Cognitive Measures	*M*	*SD*	*M*	*SD*	*p*	*d*	*M*	*SD*	*M*	*SD*	*p*	*d*
Purdue Pegboard	11.8	1.8	12.5	1.9	.053	-.38	11.8	1.8	12.4	1.6	.060	-.35
Trail Making Test Part A	34.9	11.8	35.6	10.9	.765	-.06	32.6	9.9	31.8	8.1	.679	.09
Symbol-Digit Modalities	45.4	11.5	47.9	10.2	.275	-.23	47.2	11.4	48.2	10.0	.658	-.09
Letter Cancellation	2.2	2.9	2.2	2.5	.947	.00	1.4	1.7	1.6	1.9	.628	-.11
RAVLT Trials 1-5	42.3	8.8	43.4	9.1	.544	-.12	41.3	8.0	42.7	10.2	.440	-.15
RAVLT delayed	8.4	2.9	8.2	3.2	.842	.07	8.4	3.1	8.5	3.7	.876	-.03
FAS Initial Letter Fluency	35.4	12.8	38.5	12.5	.232	-.24	38.1	14.6	40.5	13.9	.407	-.17
CW Interference Trial 3	70.0	26.1	63.0	15.7	.112	.33	66.6	20.0	61.6	14.9	.165	.28
CW Interference Trial 4	81.5	33.0	71.9	21.0	.104	.35	75.0	24.7	71.0	23.5	.431	.17
Trail Making Test Part B	89.8	43.9	86.5	42.0	.716	-.07	87.1	36.6	73.5	25.1	.043	.43

Note: CRIQ = Cognitive Reserve Index Questionnaire; SES = Socioeconomic status (Socioeconomic indexes for areas; Australian Bureau of Statistics, 2014b); Hybrid prosthesis = total hip replacement - cemented femoral stem, uncemented acetabular cup, total knee replacement - cemented tibial component, uncemented femoral component; SF-36 PCS = Short Form (36) Health Survey, Physical Component Summary; SF-36 MCS = Short Form (36) Health Survey, Mental Component Summary; HADS = Hospital Anxiety and Depression scale; RAVLT = Rey Auditory Verbal Learning Test; CW Interference = Color-Word Interference

Standardised regression-based analyses

The 6-month cognitive test scores of control participants were regressed against their baseline scores, age, gender, IQ estimation, and follow-up interval to calculate 'predicted' 6-month follow-up scores on each cognitive test (see Table 3 for results). Baseline performance was the greatest predictor of follow-up performance on all measures with age and gender accounting for small amounts of variance on learning and motor speed (refer to Table 3). However, estimated IQ and follow-up interval did not account for any significant variance on any of the cognitive measures, indicating these variables had minimal impact on the degree of change in cognitive scores from baseline to follow-up. However it is important to note that participants were followed-up within a relatively narrow time-frame, limiting the variability within these scores

Table 6-3: Control participant regression equations for predicting neuropsychological follow-up scores

Measure	R	SE_{est}	R^2	*F*	*df*	Significant unstandardised Beta coefficients			
						Intercept	*B* (baseline)	*B* (age)	*B* (gender)
Purdue Pegboard	.72	1.12	.52	14.46	3,40	10.20	.38	-.06	.84
Trail Making Test Part A	.72	5.75	.52	43.57	1,41	13.14	.53		
Symbol-Digit Modalities	.91	4.10	.82	195.7	1,42	8.01	.85		
Letter Cancellation	.62	1.52	.38	25.62	1,42	.52	.46		
RAVLT Trial 1-5	.86	5.31	.75	60.14	2,41	22.31	.87	-.26	
RAVLT Delayed	.81	2.20	.65	78.23	1,42	.88	.92		
FAS Initial Letter Fluency	.84	7.68	.71	101.46	1,42	4.27	.95		
Color-Word Interference Trial 3	.89	6.77	.79	153.02	1,40	9.17	.84		
Color-Word Interference Trial 4	.73	16.62	.54	45.08	1,39	10.71	.84		
Trail Making Test Part B	.71	18.10	.50	38.28	1,38	31.52	.51		

Note: SEest = Standard error of the estimate; df = degrees of freedom; RAVLT = Rey Auditory Verbal Learning Test.
All regression equations were significant (p <.001).

As indicated, the TJR group had lower levels of education, socioeconomic status and cognitive reserve than the controls (see Table 2). Conceivably, these differences may impact on any change in cognitive function from baseline to follow-up. Therefore, a second set of analyses excluded seven controls that had high socio-economic status, education and cognitive reserve in order to render the TJR and control groups comparable on these variables. The exclusion of these control participants did not change the findings, therefore those analyses that were based on the full control group are discussed hereafter.

The differences between the predicted and follow-up scores of TJR patients and controls were then converted into z-scores, which were then categorised according to whether cognitive performance had 'declined' ($z < -1.64$) or was either 'unchanged or improved' ($z > -1.64$). The proportion of TJR patients and controls who fell into either category was compared (see Table 4), but all differences were small and nonsignificant, suggesting that the TJR group experienced cognitive changes that were comparable to that of the Controls. Interestingly, cognition remained relatively stable despite improvements in symptoms of depression and anxiety post-surgery (see Table 2).

Table 6-4: Proportion of total joint replacement patients and controls who experienced cognitive decline at follow-up

Measure	TJR Patients	Controls	*p*	phi
Purdue Pegboard				
Declined N (%)	6 (11.5)	2 (4.4)	.279	.13
Unchanged/Improved N (%)	46 (88.5)	43 (95.6)		
Trail Making Test Part A				
Declined N (%)	6 (11.3)	2 (4.5)	.286	.12
Unchanged/Improved N (%)	47 (88.7)	42 (95.5)		
Symbol-Digit Modalities Task				
Declined N (%)	1 (2.0)	3 (6.8)	.333	-.12
Unchanged/Improved N (%)	50 (98.0)	41 (93.2)		
Letter Cancellation (errs)				
Declined N (%)	3 (5.7)	4 (8.9)	.700	-.06
Unchanged/Improved N (%)	50 (94.3)	41 (91.1)		
RAVLT Trials 1-5				
Declined N (%)	2 (3.8)	1 (2.2)	1.00	.05
Unchanged/Improved N (%)	51 (96.2)	44 (97.8)		
RAVLT Delayed				
Declined N (%)	3 (5.8)	2 (4.4)	1.00	.03
Unchanged/Improved N (%)	49 (94.2)	43 (95.6)		
FAS Initial Letter Fluency				
Declined N (%)	1 (1.9)	2 (4.5)	.592	-.08
Unchanged/Improved N (%)	51 (98.1)	42 (95.5)		
CW Interference Trial 3				
Declined N (%)	7 (13.5)	2 (4.7)	.177	.15
Unchanged/Improved N (%)	45 (86.5)	41 (95.3)		
CW Interference Trial 4				
Declined N (%)	3 (5.9)	3 (7.1)	1.00	-.03
Unchanged/Improved N (%)	48 (94.1)	39 (92.9		
Trail Making Test Part B				
Declined N (%)	7 (14.6)	3 (7.3)	.331	.12
Unchanged/Improved N (%)	41 (85.4)	38 (92.7)		

Note: Declined = z-score < -1.64, Unchanged/Improved = z-score ≥ -1.64; RAVLT = Rey Auditory Verbal Learning Test; CW Interference = Color-Word Interference Test

To overcome partitioning of variance than can occur by treating data categorically the mean SRB z-score for TJR patients and controls were compared. As shown in Table 5 there were no significant differences on nine of the ten measures. The only difference was seen on the Trail Making Test Part B (TMT B) with TJR patients showing a greater magnitude of decline on retest. Although this difference equated to a moderate effect size (d=-.49), the results suggest that the cognitive changes seen in TJR patients six months after surgery were comparable to those seen in healthy controls.

Table 6-5: Mean pre- to post-surgery change in cognitive scores among total joint replacement patients and controls

Test	TJR Patient *z*-score *M* (SD)	Control z-score *M* (SD)	*p*	*d*
Purdue Pegboard	-.25 (1.10)	-.02 (.96)	.211	-.22
Trail Making Test Part A	-.15 (1.24)	.02 (.99)	.453	-.15
Symbol-Digit Modalities Task	.18 (1.12)	-.00 (.99)	.406	.17
Letter Cancellation	.10 (.99)	-.01 (.98)	.597	.11
RAVLT Trials 1-5	.04 (1.03)	.03 (.98)	.971	.01
RAVLT Delayed	-.07 (1.04)	.03 (1.00)	.628	-.10
FAS Initial Letter Fluency	.05 (1.09)	-.00 (.99)	.808	.05
CW Interference Trial 3	.15 (2.08)	.00 (.98)	.661	.09
CW Interference Trial 4	.18 (.99)	-.04 (1.00)	.310	.22
Trail Making Test Part B	-.51 (1.33)	.04 (1.01)	.034	-.49

Note: RAVLT = Rey Auditory Verbal Learning Test; CW Interference = Color-Word Interference Test.

Predictors of pre- to postoperative cognitive change.

Although there was only minimal evidence of POCD in the TJR patients when their cognitive scores were compared to those of controls, it remained of interest to assess whether pre- to postoperative change in cognition among TJR patients was related to cognitive reserve and other variables often associated with POCD. The z-scores for TMT B were used for these analyses as this was the one measure on which TJR patients experienced significantly more decline at follow-up than controls.

Of primary interest was whether the decline in TMT B scores could be predicted by cognitive reserve. The Cognitive Reserve Index total score and the TMT B z-score did not correlate significantly, $r(48)=.215$, $p=.142$, nor was there a significant relationship with any of the Cognitive Reserve Index subscores. The threshold theory of reserve suggests that the relationship between cognitive reserve and cognition may be nonlinear, with reserve only being protective against decline until a threshold of pathology is reached (S. M. Sawrie et al., 2000). A variety of nonlinear models were therefore also used to examine the relationship between the Cognitive Reserve Index total and TMT B z-scores, however no evidence of a relationship was found. Lastly, the Cognitive Reserve Index total score did not correlate significantly with any of the other cognitive measures.

In the absence of a relationship between cognitive reserve and cognitive performance, an additional exploratory analysis was conducted to investigate whether cognitive reserve predicted pre- to postoperative change in TMT B performance in a subgroup of patients who experienced either a marked improvement or decline in their performance. To this end, the 10 TJR patients who experienced the greatest improvement pre- to post-surgery (had the highest z-scores, range: 1.70 to .68) were compared to the 10 patients who experienced the greatest decline (had the lowest z-scores, range -4.41 to -1.53) using an independent groups t-test. Patients who experienced the greatest improvement had significantly higher cognitive reserve

(M=119.4, SD=15.4) compared to those who experienced the greatest decline (M=106.8, SD=8.4; t(18) =-2.28, p=.053, d=-1.02). Notably these two groups did not differ significantly on their baseline TMT B performance.

Finally, variables that have previously been associated with POCD were also considered in relation to cognitive change. Surgery (hip vs knee: t(46)=-.56, p = .578) and anaesthesia (regional, general, combination: F(2,45)=3.2, p=.728) type were not significant predictors of cognitive change pre- to post-surgery. Moreover, the number of medications (pre-operative: r=.166, n=48, p=.259; postoperative; r=.196, n=48, p=.182), pain levels, and pre-operative Charlson Comorbidity Index scores (r=-.178, n=48, p=.227) did not correlate significantly with cognitive change pre- to post-surgery. Lastly, although the TJR and controls differed in terms of their pre-operative SF 36 Physical Component Summary Score, (r=-.010, n=46, p=.950) and their depression, (r=-.091, n=46, p=.546) and anxiety (r=-.111, n=46, p=.463) scores, none of these variables were significantly associated with cognitive change.

Discussion

This study aimed to evaluate the occurrence of POCD following TJR using methodological and statistical techniques chosen to address limitations noted in previous research. Most importantly, this study used a control group, which was matched to the patient group in terms of age, gender, IQ, physical health and baseline cognitive function; thereby minimizing the confounding effects of pre-existing group differences. Furthermore, this study used standardised regression-based methods to investigate POCD, which controls for practice effects, regression to the mean and measurement error; all of which can occur as a consequence of repeated cognitive assessments. This methodology also provided a statistically rigorous basis for defining cognitive decline, such that the magnitude of decline was unlikely to have occurred by

chance alone. A battery of cognitive tests to was used to ensure that a variety of cognitive domains were evaluated using measures to detect subtle cognitive changes. Finally, cognitive reserve was assessed to determine whether POCD was moderated by the cognitive resources available to a person prior to their surgery.

The results of the current study provided minimal evidence of POCD among TJR patients 6-months post-surgery when compared to controls. Indeed, patients only showed significantly greater decline on the TMT B – when compared to their healthy peers. There were no significant differences on any other measure. This may suggest that TJR patients experience continuing problems in specific areas, such as cognitive flexibility and set switching (Lezak, Howieson, Bigler, & Tranel, 2012). It has previously been suggested that TMT B scores are more sensitive to cognitive dysfunction than other tests (Bonner-Jackson et al., 2013; Burgess, Alderman, Evans, Emslie, & Wilson, 1998), which may explain the lack of change in the other measures used here (i.e. Colour-Word Interference, FAS Fluency). However, it is also possible that the TMT B finding was spurious, as the likelihood of such a finding from ten measures (Type 1 error) is estimated to be 40% (Raymond, Hinton-Bayre, Radel, Ray, & Marsh, 2006).

These results contrast with those reported by a number of previous studies (Deo et al., 2011; Evered, Scott, Silbert, & Maruff, 2011; Gray et al., 2008; Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011). However, many of these studies failed to use a control group (Deo et al., 2011; Gray et al., 2008; Koch et al., 2007; Rodriguez et al., 2005) and, consequently, could not determine whether any pre- to post-surgery change was greater than would be expected in the absence of surgery. Second, there have been variations in the length of follow-up interval. Earlier postoperative assessments may be more likely to detect POCD when patients have not yet fully recovered from surgery. Indeed, the two studies that used a control group and reported significant numbers of POCD (Evered et al., 2011; Salazar et al., 2011)

performed their assessments three months after surgery, when they may still have been experiencing functional limitations (National Institute of Arthritis and Musculoskeletal and Skin Diseases, 2013) and using pain medications (Holt, 2015). It may be that the POCD detected by these studies was transient; subsiding when the TJR patient experienced less pain and disability.

This study also examined whether cognitive reserve could predict the magnitude of any pre- to postoperative cognitive change that occurred. Potentially, patients with lower levels of cognitive reserve are more vulnerable to POCD. However, this could only be explored to a limited degree due to the minimal change in cognitive function that occurred within the TJR patient group. Nonetheless, a relationship between cognitive reserve and the magnitude of postoperative change on TMT B performance only emerged when the subset of cases who experienced the most extreme outcomes was examined separately. Specifically, the pre-operative cognitive reserve of the ten TJR patients with the lowest TMT B z-scores (experienced the greatest decline) was substantially lower (large effect size) compared to the ten TJR patients with the highest TMT B z-scores (experienced the greatest improvement). This suggests that greater cognitive reserve may be protective against decline by minimizing the effect of brain pathology on cognition, potentially through adaptive and compensatory strategies (Staff, 2012; Stern, 2009). Alternatively, patients with greater cognitive reserve may benefit more from test practice, thereby demonstrating greater cognitive improvement post-surgery compared to patients with lower reserve. However, no relationship between cognitive reserve and TMT B z-scores was detected among controls.

The results of this study suggest that, at most, TJR patients only experience POCD to a very limited degree six months after surgery, with the small decline that was observed potentially being a chance finding. Importantly, these data imply that patients can expect to make a good cognitive recovery in the long term and that the

POCD reported soon after surgery (Duggleby & Lander, 1994; Gray et al., 2008) may be transient. Future research should use standardised regression-based methodology, to determine whether POCD occurs in TJR patients pre-discharge and in the early months post-surgery. In addition, cognitive reserve predicted postoperative cognitive change in a subset of TJR patients. This suggests that cognitive reserve may have a positive impact on the cognitive recovery of some patients and may be a possible target for intervention studies.

There are a few limitations to consider within this study. First, it was not possible to measure cerebral microemboli in the current study. Consequently, it was not possible to determine whether and absence of POCD was attributable to the fact that the current sample did not sustain any brain damage. Were the current findings to be replicated in a sample that had significant embolic release, it would suggest that cerebral microemboli are unrelated to POCD. Ideally, future research would confirm the presence of brain pathology, using transcranial doppler imaging technology (Edmonds et al., 2000; Rodriguez et al., 2005). It would then be beneficial to investigate whether other variables, such as cognitive reserve, moderate the relationship between brain damage and POCD. Second, caution is required when generalizing these findings to the broader TJR patient population. The relatively young lower age limit (≥ 50 years) used here may have resulted in a younger patient demographic, although the mean age is comparable to previous research (M=71.6, SD=3.4; Scott et al., 2014). It is therefore possible that the findings may differ in an older sample. Although the TJR patients had lower levels of cognitive reserve, than the control group, significantly higher levels of reserve than the general population (Nucci et al., 2011; M=100, SD=15; $t(53)=6.925$, $p<.001$). Moreover, the lower reserve of the TJR group may partially reflect the fact that osteoarthritis limited their ability to engage in recent work and leisure activities; thus other measures may be more appropriate in this context. Indeed the TJR and Control groups were comparable on

the education subscales suggesting that reduced work and leisure activity were the main contributing factors. If cognitive reserve protects against POCD, then the assessment of a sample with higher-than-average reserve may underestimate the degree to with POCD occurs among the broader TJR population. Third, the lack of a surgical control group meant that the current findings cannot specifically be attributed to TJR surgery. Ideally, a surgical control group would be very similar to the TJR group with regard to demographics, pre- and post-surgical pain and function, surgical details, and the length and nature of recovery (Slade, Sanchez, Townes, & Aldea, 2001). A surgical control group was considered, but was not feasible here.

Overall, this study only found very limited evidence of POCD in TJR patients six months after their surgery. These results contrast with some previous research into POCD, potentially due to different study designs, and highlight the importance of conducting methodologically and statistically rigorous research. This study also provided some preliminary support for the cognitive reserve hypothesis, as reserve predicted changes in the performance of TJR patients who experienced the greatest change (either decline or improvement) in their cognitive performance pre- to post-surgery. However, the limited POCD among the patient sample made it difficult to explore the predictive qualities of cognitive reserve. Ultimately, this study suggests that TJR patients do not experience substantial POCD after TJR, which is a positive outcome for patients. Further research using objective measures of brain pathology (e.g. transcranial doppler imaging) is needed to advance this area, as is research that explores the predictive value of cognitive reserve in other samples where POCD has been reported, such as elective cardiovascular surgery (Funder et al., 2009).

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Appendices

Table 6-A: Baseline data for total joint replacement patients who completed the study and those lost to attrition

	Retained (*N* = 53)		Lost to Attrition (*N* = 14)			
	M	*SD*	*M*	*SD*	*p*	*d*
Age	70.0	7.2	64.9	6.1	.019	.76
Years of Education	11.1	2.9	11.7	3.2	.460	.20
IQ Estimation	106.0	9.9	101.4	13.1	.154	.40
CRIQ (total)	113.4	14.1	114.9	20.4	.762	.09
SES Decile (1-10)	5.3	2.5	5.9	2.5	.434	-.24
Charlson Comorbidity Index	3.9	1.1	3.9	2.1	.960	.00
Number of medications	4.5	3.0	5.3	3.1	.400	-.26
Bodily Pain subscale (SF-36)	30.2	15.6	24.1	12.3	.179	.43
SF-36 PCS	31.7	6.3	31.0	5.7	.693	.12
SF-36 MCS	51.7	10.8	45.8	10.2	.079	.56
HADS depression	4.6	3.2	5.6	2.5	.271	-.34
HADS anxiety	6.5	3.6	9.0	3.8	.023	-.62
	N	*%*	*N*	*%*	*p*	*phi*
Female	31	58.8	7	50.0	.763	.07
Married/Defacto	*35*	*66.0*	*9*	*64.3*	1.00	-.02
HADS depression (% ≥ 8)	8	15.7	4	28.6	.217	.14
HADS anxiety (% ≥ 8)	18	35.3	9	64.3	.069	.24
Cognitive Measures	*M*	*SD*	*M*	*SD*	*p*	*d*
Purdue Pegboard	11.8	1.8	11.6	1.8	.810	.11
Trail Making Test Part A	34.9	11.8	38.2	9.9	.336	-.30
Symbol-Digit Modalities	45.4	11.5	43.0	7.5	.488	.25
Letter Cancellation	2.2	2.9	2.3	3.0	.929	-.03
RAVLT Trials 1-5	42.3	8.8	41.3	10.3	.715	.10
RAVLT delayed	8.4	2.9	7.6	4.0	.545	.23
FAS Initial Letter Fluency	35.4	12.8	32.9	11.7	.533	.20
CW Interference Trial 3	70.0	26.1	72.6	18.0	.746	-.11
CW Interference Trial 4	81.5	33.0	79.3	22.1	.832	.08
Trail Making Test Part B	89.8	43.9	118.0	68.7	.198	-.49

Note: CRIQ = Cognitive Reserve Index Questionnaire; SES = Socioeconomic status (Socioeconomic indexes for areas; Australian Bureau of Statistics, 2014b); SF-36 PCS = Short Form (36) Health Survey; Physical Component Summary; SF-36 MCS = Short Form (36) Health Survey, Mental Component Summary; HADS = Hospital Anxiety and Depression scale; RAVLT = Rey Auditory Verbal Learning Test; CW Interference = Color-Word Interference

Chapter 7. Discussion

This thesis outlined the results of four studies that examined the cognitive and psychological outcomes of elderly patients who have undergone TJR. Specifically, in three separate meta-analyses, this thesis evaluated: a) the incidence and severity of POCD after TJR; b) the incidence of delirium after TJR and the impact of different sample characteristics and measures of delirium on the reported rates; and c) the prevalence of clinically significant levels of depression and anxiety pre- and post-surgery, and the change in the number of depression and anxiety symptoms pre- to post-surgery. This thesis also documented the findings of a clinical study that used a pre- post-surgery design and SRB methodology to investigate the incidence and severity of POCD following TJR, and whether cognitive reserve was related to POCD after TJR.

This Chapter summarises the main findings from the four studies and then discusses the methodological strengths and limitations of each. The clinical implications of these findings and suggestions for future research examining the cognitive and affective outcomes after TJR are then considered.

Summary of Findings, Strengths and Limitations

Study 1

Study 1 (Chapter 3) examined the incidence and severity of POCD in TJR patients because previous research has provided mixed results, making it difficult to reach any conclusions regarding the risk of POCD after TJR. This meta-analysis combined data from 17 studies, with 1089 TJR patients and 89 healthy controls. Individual studies were grouped and analysed according to whether the study examined TJR patients only or TJR patients and controls (single-sample pre- and post-surgery design; two-sample pre- and post-surgery design), by the length of follow-up (pre-discharge, 3-6 months post-surgery), and according to the type of cognitive test used.

Unfortunately, it was not possible to determine the incidence of POCD because all studies used different definitions of POCD. Consequently, only group data that were presented as means and standard deviations could be meaningfully combined and analysed to determine whether any change in cognitive performance occurred pre- to post-surgery

Prior to hospital discharge, patients who had undergone TJR experienced a decline in their performance on the Mini Mental Status Examination, a brief cognitive screening tool, but no such decline was evident in the long-term (3 - 6 months post-surgery) on any of the measures. However, as there was very little data from control participants, it was not possible to determine what impact repeated testing may have had on post-surgical cognitive performance of TJR patients. Consequently, it is not possible to confirm the presence or absence of POCD at 3 to 6 months post-surgery on the basis of these data. In addition, there was preliminary evidence that, compared to controls, patients experienced a greater decrease in their verbal recall pre-discharge, but not at 3 months. However, as this finding was based on only two studies, this needs to be explored further. Overall, this meta-analysis highlighted the need for researchers to: use a control group, a consistent and meaningful definition of POCD, provide both individual and group data, and use measures that are appropriate for the assessment of POCD.

There are strengths and limitations of this Study 1 that also warrant noting, in addition to those discussed in Chapter 3. A significant strength of Study 1 was the use of meta-analytic techniques in the evaluation of POCD in elderly TJR patients. Meta-analyses are considered to be superior to other types of literature review (e.g. narrative or systematic reviews) because they use methodical and replicable techniques (Lipsey & Wilson, 2001). As meta-analyses increase statistical power, they can often detect relationships that are not evident through individual studies or other forms of research summary (Lipsey & Wilson, 2001). In addition, meta-analyses can provided guidance for future research because they can determine whether a research question has been

sufficiently answered, or whether outstanding questions remain (Borenstein, Hedges, Higgins, & Rothstein, 2011).

Another strength of Study 1 was the strict inclusion criteria that were used in the selection of eligible studies. Specifically, studies were included only if they recruited TJR patients exclusively, as opposed to revision TJR, 'elective orthopaedic samples' or 'non-cardiac elective samples.' Studies were also excluded if the patients could not be deemed 'elderly' (i.e. aged 50 or greater). Cognitive assessments needed to be conducted both pre- and post-surgery using standardised neuropsychological measures (Berger et al., 2015) to ensure a reliable assessment of POCD. These criteria ensured that eligible studies were sufficiently comparable and could be validly combined into a meta-analysis.

This study also provided a comprehensive review of the literature on POCD after TJR. Search strategies were kept broad to capture the maximum number of studies. In addition, authors were contacted with requests for data when an otherwise eligible study did not include the requisite data for effect size calculation.

However, there are also a number of limitations that also need to be considered. Most importantly, some significant limitations were identified in the studies that were included within this meta-analysis. These require further examination because future research needs to address these problems in order to determine the risk of POCD after TJR.

A reliable diagnosis of POCD requires both pre- and postoperative assessment (Deiner & Silverstein, 2009), therefore confounds that arise with repeated cognitive assessment must be accounted for (Sawrie, Chelune, Naugle, & Lüders, 1996). Results from repeated cognitive assessments may demonstrate a change in performance that is not due to any actual change in capacity (Slade, Sanchez, Townes, & Aldea, 2001). Specifically, 'practice effects' can occur whereby cognitive performance improves due to familiarity with the content and/or process (Chelune, Naugle, Lüders, Sedlak, & Awad,

1993). Although practice effects can be reduced with alternate test forms, participants remain familiar with the test procedure and may therefore still demonstrate learning pre- to post-surgery (Slade et al., 2001). Only one study (Evered, Scott, Silbert, & Maruff, 2011) accounted for practice effects in their analyses. Repeated cognitive assessments are also vulnerable to regression to the mean, whereby extreme scores tend to be closer to the 'average' score on re-assessment (Speer, 1992). Lastly, measurement error may occur, possibly from slight differences in test administration or in participants' health/mood between assessments (Kaplan & Saccuzzo, 1997). At minimum, a control group is required to account for these confounds (Murkin, Newman, Stump, & Blumenthal, 1995); however, only two of the 17 eligible studies used such a control group (Evered et al., 2011; Salazar et al., 2011).

All studies reported group or individual data. Group data - usually presented as pre- and post-surgery group means and standard deviations - can obscure cognitive decline that occurs in a subset of patients (Newman, 1995). While some patients may develop POCD and show a decline in cognitive scores post-surgery, other participants, in the absence of any POCD, would likely demonstrate test practice effects. When all patients scores are combined into one set of pre- and post-surgery means, the results may suggest minimal change for the group overall (Newman, 1995; Slade et al., 2001).

Conversely, individual data measures the degree of cognitive change that has occurred for each patient using their pre-operative performance as a form of control (Murkin et al., 1995). Individual patients were typically categorised as either impaired or not impaired, based on the degree of cognitive change they have experienced pre- to post-surgery. Therefore, individual data may be more appropriate for the measurement of POCD (Murkin et al., 1995; Newman, 1995). Notably, this meta-analysis found that studies that used group data often found no evidence of POCD (e.g. Jones et al., 1990; Nielson et al., 1990; Patel, Stygall, Harrington, Newman, & Haddad, 2010), while studies that examined individual change reported evidence of POCD (e.g. Deo, West, Butcher, &

Lewis, 2011; Koch et al., 2007; Salazar et al., 2011). However, a consistent statistical definition of the degree of decline needed to constitute 'impairment' is required to meaningfully combine results from studies that have reported individual data. It was identified, at the outset that many studies have varied in the definition that they adopted, but it was surprising to find that none used comparable definitions. Ultimately, a consistent and meaningful definition of POCD must be adopted in future research to further advance the field.

This meta-analysis also found that studies often did not provide important patient (e.g. demographics and health data) or surgical (e.g. anaesthetic type, admission length, implant type, surgical approach) information. This made it difficult to determine how comparable patient samples were to one another and it was not possible to determine whether patient or surgical characteristics influenced the risk of POCD. Ideally, studies should provide data for as many potentially relevant factors as possible.

Finally, although comprehensive, this meta-analysis was not an exhaustive review of the literature. Some studies were not included because they did not provide data that could be combined into a meta-analysis and were either not contactable, or were published too long ago to request additional data. Other studies assessed a broader category of patients that are likely to have included, but were not limited to, TJR patients (e.g. 'elective orthopaedic' samples).

Study 2

The second meta-analysis (Chapter 4) examined the incidence of delirium after TJR because the wide range of rates reported in the existing literature (0 - 81%) made it difficult to establish the overall risk of delirium after TJR. It was also of interest to investigate whether differences in the samples that were recruited and the methods that were used to assess delirium contributed to this variation. Data for 2895 TJR patients from 24 studies were examined. The overall incidence of delirium after TJR was 17%. Studies were further analysed according to the operated joint (hip, knee), whether

patients with pre-existing cognitive impairment were included, the type of anaesthetic used (general, regional, combination), and differences in the assessment of delirium (e.g. the measure used; frequency of assessment). Interestingly, the rates of delirium did not differ significantly when grouped by these variables. Overall, this meta-analysis revealed that delirium is a common complication of TJR and is seen in approximately one in six patients, suggesting that orthopaedic healthcare professionals should be familiar with its risk factors (e.g. age, severe/multiple comorbid conditions, polypharmacy, sleep deprivation, dehydration; Inouye, 2006)) , as well as practices to manage or treat delirium (e.g. reorientation, maintenance of activity and mobility, review of medications, treatment of infections; Inouye, 2006).

There are also further strengths and limitations of this study beyond those described in Chapter 4 that require further consideration. This study provided an update to a previous meta-analysis that examined the incidence of delirium after elective orthopaedic surgery, (Bruce, Ritchie, Blizard, Lai, & Raven, 2007), although the current study focused specifically on TJR. Since the publication of Bruce et al., there has been a substantial increase in the number studies on delirium. Therefore, this study was also able to expand upon the findings of Bruce et al. on some of the potential explanations for the variation in the reported rates of delirium.

The current study also used strict inclusion/exclusion criteria to ensure that patients who underwent TJR from different studies were as comparable as possible. Specifically, all studies had to use a sample that was reasonably elderly (≥50 years of age), and examined TJR patients exclusively or provided separate data for this group of patients. Eligible studies were also restricted to those that based the assessment of delirium on standard Diagnostic and Statistical manual of Mental Disorders (American Psychiatric Association, 2013), or International Classification of Disease criteria (World Health Organization, 1992). This is important, given the high likelihood of misdiagnosis of delirium when validated diagnostic tools are not used (Alcover, Badenes, Montero,

Soro, & Belda, 2013). Therefore, studies were excluded if they did not report how delirium was assessed, if the assessment was based on a retrospective examination of medical notes, or if they assessed delirium using a non-delirium specific measure.

This meta-analysis also had some limitations that warrant attention. First, it was restricted by what data were reported. Potentially relevant details such as age, comorbidity, or surgical factors were often either not reported or provided in an inconsistent manner. This reduced the capacity of this meta-analysis to investigate factors that may impact the risk of delirium and to conduct any multivariate analyses to consider the effect of multiple variables simultaneously. This is unfortunate because the cause of delirium is likely to be multifactorial (Bruce et al., 2007), and multivariate analyses can be useful in separating the influence of multiple variables.

In addition, this meta-analysis cannot be considered exhaustive. Several studies were excluded because samples were not limited to TJR patients (e.g. used an 'elective orthopaedic sample') or did not establish specific age requirements. It is likely there were many eligible TJR patients within these samples; however, these data could not be included within this study.

Study 3

The third meta-analysis (Chapter 5) assessed depression and anxiety in patients who underwent TJR before and after surgery. Similar to the literature on cognitive outcomes after TJR, existing research has yielded mixed results, making it difficult to gain an overall understanding of the prevalence and severity of depression and anxiety symptoms in this patient group. This meta-analysis combined data for 4045 TJR patients and 55 healthy controls from 26 studies. Results were divided according to the type of data that were reported (the proportion of patients with clinically significant levels of depression and anxiety, or group means and standard deviations that summarise the number/severity of symptoms), the follow-up interval (pre-discharge, 6-12 weeks, 6 months, and 9-12 months), and whether the study contained TJR patients only or TJR

patients and a control group (single sample pre- post-surgery design, or two sample pre-post-surgery design). Surprisingly, only a limited number of studies reported prevalence rates. Approximately 23% of TJR patients experienced clinically significant depression prior to surgery, with the rate being 22% 6 to 12 weeks post-surgery, and 13% one year after surgery. Unfortunately, the average prevalence of anxiety could not be estimated as only four studies provided these data, and they varied too much to be meaningfully combined.

As only one study recruited a control group, the interpretation of the group data were limited because no reliable comparisons could be made between TJR patients and their healthy peers. No clinically significant changes to symptoms of depression or anxiety were evident pre- to post-surgery, although statistically significant decreases in depression were noted onwards from 6 to12 weeks post-surgery and for anxiety from pre-discharge onwards. It is not clear how these changes in symptoms (or lack thereof) compare to the general population. Patients who underwent TJR did not show any clinically significant differences in the change in symptoms pre- to post-surgery compared to controls; however, these findings were only based on the results of one study. Overall, the data suggest that a high proportion of patients experience clinically significant levels of depression following TJR surgery and that patients, as a whole, only experience a modest improvement in symptoms pre- to post-surgery, although this needs to be confirmed through further research that compares these changes to those within a control group.

Some strengths and limitations beyond those discussed in Chapter 5 warrant attention. Firstly, this study provided the first meta-analysis on depression and anxiety in patients undergoing TJR. It provided an overall summary of what can be learned from the existing literature and provided a detailed list of recommendations for future research to address the questions that remain outstanding.

Like Study 1 (Chapter 3), this meta-analysis was restricted by the data that were reported within the studies. Specifically, only one study used a control group, therefore it was not possible to draw any conclusions about how depression and anxiety symptoms in patients undergoing TJR compared to the general population. It was also not possible to determine whether any change in symptoms was attributable to TJR, specifically, or would have occurred regardless.

In addition, studies that reported the proportion of patients who experienced clinically significant levels of depression and anxiety pre- to post-surgery did not report individual change data. Therefore, it was not clear whether the patients with clinically significant levels of depression and anxiety pre-surgery, were the same patients as those post-surgery. Patients who experience high levels of psychological distress pre- and post-surgery are likely to be very different to patients who experience high levels of distress at only one of those times. Conceivably, the former group may be more likely to experience chronic depression, or perhaps are more vulnerable to the particular stressors present both pre- and post-surgery. The presentation of symptoms and the response to certain treatments are likely to differ between these patients (Ghaemi & Vohringer, 2011). Furthermore, having individual change data would have meant that the differences in pre- and post-surgery rates of depression and anxiety could have been subjected to within-subject significance testing, which was not possible with the current data.

Like the previous meta-analyses presented in this thesis, this meta-analysis was not considered exhaustive. Studies were excluded if the patient sample was not exclusively composed of TJR patients or did not provide sufficient data regarding the age of the sample. It is also possible that studies were missed in the initial literature search because measures of depression and anxiety were often incidental to the primary aims of research. It is possible that some studies did not allude to using these measures in the title or abstract and were not located in the search and screening processes.

Study 4

Chapter 6 outlined the results of a clinical study (Study 4) that was designed to address many of the gaps in the literature that were identified by Study 1; specifically to assess POCD following TJR using a meaningful definition of POCD, a healthy control group, and appropriate cognitive measures. Fifty three TJR patients and 45 healthy controls were recruited to assess POCD after TJR. Participants were assessed at baseline (pre-surgery for TJR patients) and six months later using a battery of cognitive tests. SRB methodology (Sawrie et al., 1996) was used to identify POCD. Using this methodology, a predicted follow-up score was calculated for each patient to provide an estimate of a participant's follow-up score in the absence of cognitive decline. This score was then compared with a patient's actual follow-up score. Cognitive decline was deemed to have occurred if a patient's actual follow-up score was more than two standard deviations below their predicted score (i.e. they experienced a degree of decline in performance that is statistically uncommon). TJR patients demonstrated a significantly greater decline in performance on Trails B, compared to controls; however, there is a 40% possibility that this was a chance finding (Raymond, Hinton-Bayre, Radel, Ray, & Marsh, 2006). On all other measures, the change in cognitive performance for the TJR group was comparable to that of the controls. Overall, this study revealed only minimal evidence of POCD at six months post-surgery, which is a positive outcome for TJR patients.

The second aim of Study 4 was to examine whether cognitive reserve could predict POCD after TJR. However, as the patients who underwent TJR showed limited evidence of POCD, this question remains outstanding. Although cognitive reserve did not predict Trails B performance in the whole sample, it did predict performance for a subset of patients who experienced either the greatest improvement or the greatest decline on Trails B performance. Overall, it cannot be determined from these data whether cognitive reserve can predict POCD and this question remains to be clarified

among a patient sample that demonstrates greater POCD. As described in Chapter 6, it possible that the high functioning post-surgery status of the TJR sample may be a consequence of their higher level of cognitive reserve (Nucci, Mapelli, & Mondini, 2011). Potentially, this may also explain the difference in findings between the current study and previous research that has reported POCD (Deo et al., 2011; Evered et al., 2011; Koch et al., 2007; Salazar et al., 2011).

A significant strength of Study 4 is the methodology. This was the first clinical study to use SRB methodology in the assessment of POCD after TJR. SRB methodology is superior to other forms of statistical analysis because it disentangles genuine pre – to post-surgical cognitive change, while controlling for practice effects, regression to the mean and measurement error (Sawrie et al., 1996). POCD was defined as a significant, statistically unlikely deterioration in cognitive performance pre- to post-surgery. This is a defensible and theoretically valid statistical method by which to define decline in cognitive performance and is free of arbitrarily defined cut-off points (Kneebone, Luszcz, Baker, & Knight, 2005; Sawrie et al., 1996). This study provided the requisite data for future researchers who may wish to either replicate these findings or to use data from the control sample to use SRB norms in their own clinical study (Chapter 6, Table 6-3). In addition to SRB statistics, this study also provided group data (see Chapter 6, Table 6-2) to ensure that it was comparable with previous research.

All measures used within this study were carefully selected. A cognitive test battery was used to detect subtle cognitive dysfunction that may occur in a variety of domains (Murkin et al., 1995). Tests were selected to be comparable with previous research, to cover a wide variety of cognitive domains, and to be consistent with the recommendations made by the *Statement of Consensus on the Assessment of Neurobehavioural Outcomes Following Cardiac Surgery* (Murkin et al., 1995). Many other potentially relevant details and measures were also collected, such as demographics, surgical details (patients only), smoking and drinking history, medical

history, current medication use, pain, handedness, quality of life, and depression and anxiety. These additional measures enabled an extensive examination of some of the factors that may be related to cognitive function.

Another novel aspect of this study was the assessment of cognitive reserve as a predictor of POCD. This study used the Cognitive Reserve Index Questionnaire, which provides a standardised, reliable and comprehensive assessment of multiple domains of cognitive reserve. Scores are also weighted by age (Nucci et al., 2011). Previous research has often assessed only one domain of cognitive reserve (e.g. years of education, IQ estimation) and studies have differed in terms of how each of these domains are measured.

A major limitation of this study was that patients who underwent TJR were not assessed for brain injury acquired from surgery. Unfortunately, it was beyond the resources available to this study to assess patients using neuroimaging, transcranial doppler ultrasonography, or to measure biomarkers of brain damage (e.g. the S100B protein, or glial fibrillary acidic protein) to determine whether patients had suffered any brain injury. Therefore, it is not possible to determine whether absence of brain pathology may explain the current positive results.

A second limitation of this study was the type of control group that was selected. The use of a healthy control group is recommended when only one control group can be assessed (Murkin et al., 1995); however this limits the conclusions that can be drawn. Specifically, it is not possible to determine whether TJR, as opposed to other factors - such as the type of surgery/procedure, admission to hospital, or experience of long term illness - may explain the outcomes of patients. A more detailed justification for the use of a healthy control group was provided earlier (see Preface, Chapter 6), but it remains important to keep this limitation in mind when drawing conclusions from these data.

It is not possible to determine whether the decline observed in TJR patients' Trails B performance translated to a clinically significant effect on everyday function. In

general, neuropsychological tests are believed to be moderately predictive of performance in everyday activities (Chaytor & Schmitter-Edgecombe, 2003) and Trails B has been found to have higher ecological validity, compared to some other measures of executive function (Chaytor, Schmitter-Edgecombe, & Burr, 2006). Therefore, it is possible that a moderate decline in Trails B performance may translate to a clinical deficit. Potentially, patients who lead cognitively demanding lives may be more affected by such a decline in performance. However, there was no assessment regarding the patients' views of their own postoperative cognitive function and recovery. Consequently, it is not possible determine whether the decline in Trails B performance translated to a decline in everyday function.

Another limitation of this study was the 20% (*N*=14) attrition rate among TJR patients. The majority of these patients (*N*=10) did not complete a second follow-up for medical reasons (e.g. TJR surgery was significantly delayed or cancelled, underwent second surgery prior to follow-up) or practical reasons (e.g. had moved interstate). This attrition may have impacted on the results, although statistical tests indicated that those retained and those lost to follow-up were comparable on all cognitive measures at baseline (See Chapter 6, Table 6-A). This attrition also reduced the statistical power of this study, although the impact of this was lessened by the reporting effect sizes.

Clinical Implications and Future Research Recommendations

Cognitive outcomes after total joint replacement

COMMENT3 Study 1 (Chapter 3) summarised the literature on POCD after TJR. It was found that prior to hospital discharge, patients experience a decrease in their performance on a general cognitive screen (usually the MMSE), but not on any other cognitive measures. However, this decrease in performance may actually reflect symptoms of delirium in patients, rather than POCD. Study 2 found that delirium is a

very common complication of TJR and develops in one in six patients prior to hospital discharge. The MMSE is not specifically designed to detect delirium and is not generally recommended for use in delirium assessments. Nonetheless, it can detect some symptoms typical of delirium, including inattention and disorientation (O'Regan, Fitzgerald, Timmons, O'Connell, & Meagher, 2013). Therefore, as delirium is common within one week of surgery, it is possible that the decline in MMSE performance detected pre-discharge may reflect some symptoms of delirium, rather than POCD. Furthermore, no decline in MMSE performance was evident at 3-6 months post-surgery. As delirium is usually transient, it would be expected that most of the occurrences that developed prior to hospital discharge would have resolved by this stage (Alcover et al., 2013).

Ultimately, Study 1 did not provide any firm conclusions with regard to long-term POCD after TJR and this remains an important unresolved clinical question. Therefore, the utility of this study lies in its implications for future research. Indeed, this study guided the design of Study 4, which aimed to address the gaps identified within the existing research. The results of Study 4 revealed only minimal evidence of POCD six months after TJR. This is a very positive finding, both for TJR patients themselves and for clinicians who may have concerns about the impact of surgery on long term cognition and how that may affect patient recovery. However, as previously mentioned, this contradicts the findings of several previous studies (Deo et al., 2011; Evered et al., 2011; Koch et al., 2007; Rodriguez et al., 2005; Salazar et al., 2011). It is possible that this study highlights the different results that may arise when more rigorous techniques are used.

It is also possible that the current results are a result of an especially high-functioning patient group and had they been more comparable to previous research, the results may have been similar. It is unclear why the current patient sample should be higher functioning compared to other samples. It is possible that this may reflect a difference in which patients have access to total joint replacement under different health

systems. However, it should be noted that the current findings conflict with Deo et al. (2011). This study also recruited patients from within the public health system in Adelaide, South Australia and so the patient sample would be very similar to the current sample, in terms of available health care.

Overall, the results of Study 1 and 4 suggest that patients who undergo TJR experience little, if any POCD six months after surgery. However, this finding should be confirmed through replication. It is also important to note that Study 4 cannot shed light on patients' postoperative cognitive function prior to the six month follow-up. It is possible that some patients experienced POCD at an earlier stage, which had resolved by the six month follow-up. On the basis of these findings, it is not possible to definitively conclude that POCD did not occur at any time during the postoperative period.

Future research should aim to replicate these findings using SRB methodology, as this is a better method with which to assess cognitive change (Sawrie et al., 1996). To further test the robustness of these findings, future research should also aim to recruit TJR patients of lower cognitive reserve than the sample used in Study 4. In addition, patients should also be assessed three months after their surgery because it is possible that some patients may have experienced POCD at an earlier stage (e.g. prior to discharge or within the earlier post-surgical period), with these problems having resolved by the six month follow-up. This may also explain the difference in the findings between Study 4 and the previous research that has reported POCD among TJR patients 3 months post-surgery, when compared to healthy controls (Evered et al., 2011; Salazar et al., 2011).

Ideally SRB methodology would be used more widely in all research that requires repeated neuropsychological assessments. Furthermore, the SRB techniques may also be useful in clinical settings to assist in the reliable identification of meaningful cognitive change among patients (Sawrie et al., 1996).

Study 4 also investigated whether cognitive reserve could predict POCD following TJR. As the TJR patient sample were high functioning following surgery, this question remains outstanding and no clinical implications can be drawn from these results. Cognitive reserve may still predict POCD in a patient sample that has experienced significant cognitive decline. Future research should investigate whether cognitive reserve moderates the relationship between brain pathology (either pre-existing or intra-operatively acquired) and POCD after TJR and other types of surgery. Brain pathology could be assessed using Magnetic Resonance Imaging or through testing for biomarkers of brain damage, such as the S100B protein, or glial fibrillary acidic protein (Tomaszewski, 2014). It remains of clinical interest to establish whether cognitive reserve is associated with the development of POCD among other patient groups. If such a relationship is found, then modifiable aspects of cognitive reserve (e.g. engagement in cognitively stimulating leisure activities) could be explored as a target for intervention studies to reduce the incidence of POCD among patient groups that are at risk of cognitive problems.

Study 2 (Chapter 4) established that delirium is a common complication of TJR, occurring in approximately one in six patients. As a result, delirium could be considered to be, by far, the most common in-hospital complication of TJR (Pulido et al., 2008). The development of delirium after TJR is also associated with other negative outcomes, such as an increased risk of cognitive decline and dementia, and greater long-term care requirements (Bickel, Gradinger, Kochs, & Forstl, 2008). Therefore, clinicians need to be proficient in the identification, management and treatment of delirium. They should also be aware of both the non-pharmacological and pharmacological strategies to manage patients with delirium, and what approaches are most appropriate for individual patients. Furthermore, a reduction of the modifiable risk factors for delirium should be a high priority for orthopaedic departments. Simple changes can be implemented to reduce the risk of delirium, such as ensuring all rooms have clocks, patients use their earing or

vision aids where possible, and minimising factors that may contribute to sleep deprivation (Inouye, 2006; McCusker et al., 2001). These changes may reduce the rate of delirium in patients who undergo TJR, which would also reduce the burden on their families and health professionals.

It may also be important to inform patients and their families, prior to surgery, on the nature and risk of delirium (Breitbart, Gibson, & Tremblay, 2002; O'Malley, Leonard, Meagher, & O'Keeffe, 2008). The development of delirium can be a significant source of stress for patients and families. Hospital patients who experience delirium have reported feeling fearful, anxious and depressed, and patients who experience delusions or hallucinations have reported severe distress (O'Malley et al., 2008). Patients with delirium have also reported embarrassment and concern from difficulties communicating with others. Families of patients with delirium can also become distressed and desire more information on the syndrome from the treating clinicians (O'Malley et al., 2008). In addition, nurses and carers have also reported significant distress when caring for patients with delirium due to their greater needs, and concerns about providing adequate care to patients, especially when the patient does not trust their carer and acts unpredictably (Breitbart et al., 2002). Future research should investigate whether providing patients, families, and clinicians with more knowledge of delirium leads to a reduction in the stress that is associated with its development. Potentially, if they are well informed prior, delirium symptoms may not be as shocking to patients and families, and clinicians may feel more confident in their ability to help patients with delirium.

COMMENT9 Future research may also focus on methods to reduce the risk of delirium following TJR. Research could investigate whether additional training for elective orthopaedic clinicians in the identification, management and treatment of delirium can reduce rates. Although this meta-analysis failed to find any significant risk factors for the incidence of delirium, other potentially modifiable risk factors for delirium have been identified among other patient groups via quasi-experimental and

observational studies. These risk factors include sensory impairment, lack of orientating devices, dehydration, room changes, and sleep deprivation (Inouye et al., 1999; McCusker et al., 2001). Future research may investigate whether minimising these risk factors reduces the rate of delirium following TJR.

Psychological outcomes of total joint replacement

Study 3 summarised research that assessed symptoms of depression and anxiety after TJR. With regard to the prevalence of clinically significant levels of depression and anxiety, this meta-analysis was limited by the small number of studies that reported these data, especially anxiety. However, it may tentatively be concluded that TJR patients have a higher prevalence of depression when compared to the general population, pre- and post-surgery. This may have clinical implications for patient recovery following TJR, as greater symptoms of depression may have a negative impact on physical recovery.

Group data revealed that patients who undergo TJR only experience modest improvements in their symptoms of depression up to one year post-surgery. This suggests that the situational risk factors for depression that are associated with TJR surgery - such as pain, poor physical function, and stress - may only have a limited influence on depression within this patient group. Alternatively, it is possible that new situational stressors arose after surgery which may hinder improvement in psychological symptoms that would otherwise be expected as a consequence of a reduction in pain and disability. For example, during recovery, patients may begin to feel distressed about the rate of their progress. Furthermore, if patients experience any transient POCD or delirium in the postoperative period, this may also cause psychological distress, especially if the patient has ongoing concerns about the meaning or implications of their cognitive symptoms. Future qualitative research may help to understand the situational causes of psychological distress during recovery from TJR surgery. In addition, research should explore whether the treatment of patients with clinically significant levels of

depression (and for anxiety) during this time may lead to improved pain and functional outcomes.

Finally, Study 3 revealed many outstanding questions regarding psychological symptoms in TJR patients, specifically about the rate of clinically significant levels of depression and anxiety, and the severity of symptoms relative to the general population. Research should now aim to address these gaps by adopting more methodologically rigorous research designs. Specifically, studies should use a control group and provide separate data for patients who experience clinically significant levels of symptoms, because these patients are likely to be of greatest clinical concern. Structured interviews (e.g. The Structured Clinical Interview for DSM-5; First, Williams, Karg, & Spitzer, 2015) could also be used to identify patients with different types of depression and anxiety disorders, as they are defined in the DSM. Finally, it would also be beneficial to report as many factors as possible that are potentially related to symptoms of depression and anxiety, such as pain, function, medications, and co morbid conditions to help unpack the causes of depression and anxiety symptoms in patients who undergo TJR.

Although it was not the primary aim of the study, depression and anxiety symptoms were also measured in Study 4 to account for their potential effect on cognition in TJR patients (Ghoneim & O'Haram M. W., 2016). A greater proportion of TJR patients reported clinically significant levels of symptoms prior to surgery, compared to the healthy controls, although the analysis was not sufficiently powered to confirm whether this difference was significant. Controls also had a high baseline rate of clinically significant anxiety, compared to the rates typically found in the general population (Australian Bureau of Statistics, 2008). However, at the six month follow-up, both patients and controls reported levels of symptoms that were more comparable to the general population. It is likely that the increase in anxiety symptoms were, at least in part, a response to the stress associated with surgery, although it is not clear why the control participants experienced greater levels of anxiety at baseline. It is possible that

the HADS may overestimate anxiety levels when used in a healthy sample, as opposed to a medical outpatient sample, although the psychometric properties of the scale are reportedly comparable when used with the general population and medical samples (Bjelland, Dahl, Haug, & Neckelmann, 2002). It is also possible that, at the first assessment, both patients and controls were more anxious when completing the HADS, having just undergone cognitive testing, which can be stressful. At the second assessment, patients and controls may have been less nervous because they knew what to expect from the testing session.

Some of the symptoms of depression and anxiety – such as poor concentration, low energy, restlessness, and poor sleep – may also affect cognitive ability. Even mild symptoms of anxiety have been found to negatively affect the performance of healthy older adults when completing cognitive tests (Beaudreau & O'Hara, 2009), especially when they occur with mild symptoms of depression (Beaudreau & O'Hara, 2009; Kizilbash, Vanderploeg, & Curtiss, 2002). Although symptoms of depression and anxiety are not thought to cause POCD (Khatri et al., 1999), if they develop after surgery they may mimic, or further worsen a POCD deficit that has arisen from other causes. Importantly, patients who suffer depression and anxiety are more likely to report experiencing cognitive problems, regardless of whether there is objective evidence of a deficit on cognitive tests (Khatri et al., 1999). If patients believe they are impaired, this could have a negative impact on their level of functioning. This may, in turn worsen their psychological symptoms.

Summary

This thesis presented four independent studies that examined cognitive and psychological outcomes after TJR. Currently, the literature has yielded mixed findings on these problems, therefore, Studies 1, 2 and 3 summarised the literature on POCD, delirium, and depression and anxiety, respectively, to utilise the available literature to

determine the risk of these problems in older patients who undergo TJR. Study 1 was limited in the conclusions that could be drawn regarding POCD following TJR and reinforced the need for methodologically and statistically rigorous research in this field. Delirium, on the other hand was found to a very common complication of TJR and future research now needs to investigate strategies to minimise its occurrence. Preliminary findings suggest that patients who undergo TJR also experience clinically significant levels of depression and anxiety more frequently than the general population, and experience a modest improvement in symptoms pre- to post surgery. However, further methodologically rigorous research is required to confirm these findings.

The gaps in the literature identified by Study 1 assisted in the development of a clinical study (Study 4) that investigated the incidence and severity of POCD, while addressing the methodological problems identified in existing research. It was found that patients who underwent TJR were largely comparable in their cognitive performance to healthy controls six months after their surgery. This finding contradicts much previous research (Deo et al., 2011; Evered et al., 2011; Koch et al., 2007; Salazar et al., 2011), but replication is needed. Nevertheless this outcome is positive for patients who undergo TJR. Study 4 also investigated whether cognitive reserve could predict POCD after TJR, but was limited by the fact that POCD was very limited, therefore this question remains outstanding.

Together, these studies have evaluated and updated a field of research that was previously difficult to interpret due to the wide variation in study methodology and findings. They have also outlined what remains to be investigated. Overall, these findings have contributed to a greater understanding of cognitive and psychological outcomes of TJR, which is likely to be important in efforts to maximise patient recovery.

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