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TITLE PAGE

TITLE: Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis

RUNNING TITLE: Predictors of delirium post-hip fracture surgery

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ABSTRACT

Objective: Delirium is one of the most common complications following hip fracture surgery in older people. This study identified pre- and peri-operative factors associated with the development of post-operative delirium following hip fracture surgery.

Methods: Published and unpublished literature were searched to identify all evidence reporting variables on patient characteristics, on-admission, intra-operative and post-operative management assessing incident delirium in older people following hip fracture surgery. Pooled odds ratio (OR) and mean difference (MD) of those who experienced delirium compared to those who did not were calculated for each variable. Evidence was assessed using the Downs and Black appraisal tool and interpreted using the GRADE approach.

Results: 6704 people (2090 people with post-operative delirium) from 32 studies were analysed. There was moderate evidence of nearly a two-times greater probability of post-operative delirium for those aged 80 years and over (OR: 1.77; 95% CI: 1.09, 2.87), whether patients lived in a care institution pre-admission (OR: 2.65; 95% CI: 1.79, 3.92), and a six-times greater probability of developing post-operative delirium with a pre-admission diagnosis of dementia (OR: 6.07, 95% CI: 4.84, 7.62). There was no association with intra-operative variables and probability of delirium.

Conclusion: Clinicians treating people with a hip fracture should be vigilant towards post-operative delirium if their patients are older, have pre-existing cognitive impairment and poorer overall general health. This is also the case for those who experience post-operative complications such as pneumonia or a urinary tract infection.

Keywords: Fractured neck of femur; proximal femoral fracture; anaesthetic; surgical optimisation; orthogeriatric care; delirium

Word Count: 3573

PROSPERO REGISTRATION: CRD42016027845

INTRODUCTION

Delirium (sometimes called 'acute confusional state') is characterised by disturbed consciousness, cognitive function or perception, which has an acute onset and fluctuating course. The incidence of post-operative delirium following hip fracture surgery has been estimated to be between 4% and 53%, and is the most common surgical complication for older people following surgery (Rizk *et al*., 2016). The consequences of experiencing delirium include higher mortality rates, hospital-acquired complications, persistent cognitive impairments, poor functional recovery after surgery, and increased healthcare costs (Martocchia *et al*., 2015). Patients undergoing hip fracture surgery will experience delirium three-times more often than those who have non-orthopaedic surgery procedures (Jagmin, 1998). Given these consequences and the high prevalence of delirium following hip fracture surgery in this population, the identification of people at risk and the implementation of preventative strategies to reduce mortality or morbidity is highly desirable.

Whilst the pathophysiological mechanisms remain unclear, it is universally acknowledged that a number of important factors are associated with increased risk of delirium following surgery (Bitsch *et al*., 2006). These have included: older age; dementia and memory problems; and visual or hearing difficulties (Adunsky *et al*., 2003; Bruce *et al*., 2007).

Previous systematic reviews have explored possible factors which may predict which people experience post-operative delirium following hip fracture surgery (Adunsky *et al*., 2003; Bruce *et al*., 2007; Oh *et al*., 2015; Yang *et al*., 2016). However, a number of papers have been published in the last 12 months which may provide additional data to support or refute previous conclusions. Furthermore previous systematic reviews have not explored the relationship between intra-

operative factors and post-operative delirium. The aim of this study was to examine the available literature and determine the effects of pre-, intra- and early post-operative factors on the incidence of post-operative delirium in older people who undergo surgery for hip fracture.

MATERIALS AND METHODS

The systematic review was registered prior to commencing the search strategy (Registration number: CRD42016027845). The protocol deviations were: i) data on post-operative variables were collected to assess their relationship to the development of post-operative delirium; ii) the Cochrane Risk of Bias tool was not used to appraise the literature given that no randomised controlled trials were identified during the search strategy; and iii) odds ratio rather than relative risk were used to assess the probability of a candidate variable being associated with the development of post-operative delirium.

Search Strategy

An electronic search was performed using the following databases: Web of Science v5.19 (science and social science citation index), OVID MEDLINE(R) in-process & other Non-Indexed Citations & Ovid MEDLINE(R), EMBASE, the Cochrane Library (Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews) and the University of York Centre for Reviews and Dissemination Database. We also searched for unpublished and grey literature using the databases/trial registries: World Health Organization Clinical Trial Register, EU clinical trials register, ClinicalTrials.gov and OpenGrey. The search terms for MEDLINE are presented in **Supplementary Table 1**. These were adapted for each specific search database. All searches

were performed from database inception to 1st June 2016. A hand search was performed of the reference lists of all relevant reviews and relevant primary articles to identify any articles omitted by the electronic searches. Restrictions were not applied, such as language or age of publication. We included any studies published from 2000 to account for changes in healthcare and rehabilitation provision which were different in provision prior to this period (Smith *et al*., 2015).

Eligibility Criteria

The eligibility criteria are presented below.

Inclusion:

- Participants have undergone a surgical procedure for hip fracture fixation.
- Prospective or retrospective cohort study designs where a validated diagnostic screening tool for detecting delirium or cognitive impairment in older people was used to determine the presence/absence of delirium post-operatively.
- Randomised controlled trials (RCTs) investigating anaesthetic approaches e.g. regional anaesthesia versus general anaesthesia for older people (defined as a cohort with a mean or median aged 65 years or over) undergoing any surgical intervention for hip fracture.

Exclusion:

- Studies where a validated diagnostic screening tool has not been used to define delirium at baseline (e.g. pre-operatively).

- Mixed sample studies (e.g. hip and knee surgery) where the results for different operative type are not presented independently.
- Studies reporting patients who experience delirium tremens.

Study Identification

The titles and/or abstracts of all search results were independently reviewed by two reviewers (AC, TS). The full-texts of all those deemed potentially eligible were gathered and reviewed against the criteria by the same two reviewers. Full-texts which met the eligibility criteria and were agreed by two reviewers (AC, TS) were included. Any disagreement on study eligibility was resolved through discussion until a consensus was reached.

Data Extraction

All data were independently extracted by two reviewers (AC, TS). This was performed using a pre-defined data extraction template. Data extracted included:

Study variables: country of study origin; number of participants; number of participants with pre- and post-operative delirium; number of participants with pre-operative cognitive impairment; methods of assessing delirium.

Participant variables: mean age; sex.

Pre-operative/on-admission variables: fracture type; surgical intervention; American Society of Anaesthesiology (ASA) grade; co-morbidities (such as dementia, stroke, hypertension, diabetes, cardiac failure, renal failure, pulmonary conditions); Charlson Comorbidity Index score (CCI);

medication use/prescription pre-admission and the frequency of specific medication prescription (such as antipsychotic medications).

Intra-operative variables: medication use; use of sedation; anaesthetic type and duration; intra-operative blood pressure; intra-operative blood loss; require

Post-operative variables: length of stay; post-operative medication requirements (particularly morphine use); post-operative complications.

Outcome Measures

The primary outcome was the presence of delirium defined by a diagnostic screening tool validated for use with elderly people e.g. the Confusion Assessment Method (CAM) or delirium listed in clinical records. We planned to assess the frequency of delirium (absence or presence) pre-operatively and then at follow-up intervals of: i) initial post-operative period to Day 3 (immediate), ii) Day 4 to Day 7 (shorter-term), and iii) Day 8 to acute hospital discharge (longer-term). We assessed the risk of delirium in relation to each of the variables assessed on-admission, intra-operatively and post-operatively.

Quality Assessment

We assessed the quality of the evidence using the Downs and Black tool (Downs and Black, 1998). Critical appraisal was undertaken by one reviewer (AC) and verified by a second reviewer (TS). Disagreements were resolved through discussion with a third reviewer (JC) used to reach consensus when needed.

Data Analysis

The aim of the analysis was to determine what pre-, intra- or early post-operative (i.e. initial 72 hours) factors are associated with incident delirium in older people following hip fracture surgery. We therefore assessed the data extraction table for suitability of meta-analysis. Study heterogeneity was determined through visual examination of the data extraction table, assessing for between-study variability/similarity for participant characteristics, surgical and recovery pathway intervention, and study design and process. This was performed by three reviewers (AC, TS, JC). When there was agreement of moderate to high study heterogeneity, the results were analysed using a narrative approach. When there was low risk of study heterogeneity, a meta-analysis was deemed appropriate. In such an instance we pooled data on events of delirium at each follow-up period (initial/shorter-term/longer-term) to estimate the odds ratio (OR) of delirium for each assessment dichotomous factor. For continuous outcomes such as length of stay and blood loss, the mean difference (MD) was estimated for those who developed delirium versus those who did not. For all analyses, 95% confidence intervals (CI) and forest-plots were calculated. We estimated the statistical heterogeneity using the inconsistency variable (I^2) test. When I^2 equated to 20% or more, a random-effects model was utilised. When I^2 equated to less than 20%, a fixed-effects model was utilised. Small study publication bias was assessed using funnel plot analyses for all intra-operative factors when 10 or more datasets are presented.

Each outcome was analysed using the GRADE approach [11]. Hence each individual analysis was assessed in four domains: precision, inconsistency, indirectness of study results, and publication bias, to determine whether the evidence for each specific outcome was high, moderate, low or very low quality [11].

RESULTS

Search Results

The results of the search strategy are presented in **Figure 1**. A total of 6427 citations were identified. From these, 42 were potentially eligible. Based on the pre-defined eligibility criteria and full-text of these studies, 32 were identified as satisfying the criteria and included in the analysis.

Publication Bias

The results of the assessment for small sample size publication bias are presented as **Supplementary Figure 1**'s funnel plot. As this demonstrates, there was broadly a symmetrical funnel plot for the assessment of age, indicating a low risk of small sample size publication bias.

Quality Assessment

A summary of the Downs and Black (1998) quality assessment are presented in **Supplementary Table 2**. Although the evidence was largely of high quality, there remained considerable variability in the quality of reporting. Papers frequently reported well the aims of their studies (100%), the main outcome measures (96%), and the probability values of their inferential analyses (91%) with low attrition within their cohorts (88%). However, only 16% of the papers reported fully the specific surgical and patient pathway following hip fracture, and only 34% of papers fully reported all important adverse events for their cohorts. There was no evidence of dataset data-mining in 84% of papers and whilst 94% of papers used appropriate statistical tools, only 78% adjusted for their analyses between the delirium and non-delirium groups by length of

follow-up. Only 34% of studies adjusted for confounders which may have affected the main findings. Whilst all papers recruited cases and controls from the same population at the same time, none of the papers assessed sample size to determine if analyses were sufficiently powered.

Characteristics of Included Studies

A summary of the characteristics of the included participants are presented in **Table 1**. A total of 6792 participants were included in the review. This included 2090 people who were assessed as having experienced delirium post-hip fracture surgery, and 4614 who did not experience delirium. Participants lost to follow-up was documented in five papers (Bitsch *et al*., 2006; Björkelund *et al*., 2011; Luger *et al*., 2014; Wang *et al*., 2008; Westhoff *et al*., 2013), accounting for 88 participants in total). From those who experienced delirium, mean age ranged from 73.7 years (Chrispal *et al*., 2010; Radinovic *et al*., 2014) to 88.3 years (Mézière *et al*., 2013), whilst in the non-delirium group, mean age ranged from 71.3 years (Chrispal *et al*., 2010) to 88.4 years (Luger *et al*., 2014).

The most commonly used delirium assessment tool was the CAM (Inouye *et al*., 1990) which was used alone in 20 studies (**Table 1**). The CAM was used in conjunction with the Delirium Rating Scale-Revised-98 (DRS-R-98) tool in two further studies (Westhoff *et al*., 2013; Nie *et al*., 2012), and in addition to the DRS-R-98 and Memorial Delirium Assessment Scale (MDAS) in Watne et al (2014). The Delirium Observation Screening (DOS) tool was used in Schuurmans et al (2003), the Short Portable Mental Status Questionnaire (SPMSQ) was used in Björkelund et al (2011), whilst Luger et al (2014) used the Diagnostic and Statistical Manual of Mental Disorders (DSM-4; Fourth Edition) to assess delirium. The Mini Mental State Examination (MMSE) was used alone in two studies (Bitsch *et al*., 2006; Papadopoulos *et al*., 2012), and with the Organic Brain Syndrome (OBS) in Edlund et al (2001). Ilango et al (2016) assessed delirium through a combination of the Pain assessment in Advanced Dementia Scale (PADS), Pittsburgh Agitation Scale (PAS) and Verbal Pain Scale (VPS).

Meta-Analysis – On-Admission Variables

A summary of the meta-analysis results for variables collected on-admission are presented in **Table 2**. There was no difference in probability of experiencing post-operative delirium based on patient sex, BMI or smoking history (p≥0.07). There was moderate quality evidence to suggest a nearly two-times greater probability of post-operative delirium with those aged 80 years or over (OR: 1.77 95% CI 1.09, 2.87; N=394). There was a mean difference in age of 2.9 years between those who demonstrated delirium compared to those who did not (MD: 2.91; 95% CI: 1.89, 3.93; N=4071; **Figure 2**). There was nearly a three-times greater probability of delirium in patients who were living in institutional residential care (OR: 2.65; 95% CI: 1.79, 3.92; N= 2257; **Supplementary Figure 2**), and those with post-operative delirium had a lower MMSE score (mean: 4 points) on admission compared to those without post-operative delirium (MD: -3.52; 95% CI: -4.07, -0.73; N=1275). There was low quality evidence to suggest a three-times greater chance of delirium for those with an on-admission MMSE score of less than 24 points (OR: 3.44; 95% CI: 1.78, 6.66; N=260).

There was moderate quality evidence to suggest those with visual impairment had a two-fold greater in chance of post-operative delirium compared to those without (OR: 2.02; 95% CI: 1.02, 4.04; N=1179; **Supplementary Figure 3**). There was moderate quality evidence that on-admission comorbidities including cardiac failure (OR: 3.23; 95% CI: 1.84, 5.66; N=2120), dementia (OR: 6.07; 95% CI: 4.84, 7.62; N=2355), depression (OR: 2.61; 95% CI: 1.07, 6.34; N=905) and stroke (OR: 3.55; 95% CI: 1.56, 8.07; N=2036) increased the probability of experiencing delirium. There was low quality evidence to suggest a greater probability of experiencing post-operative delirium with a history of renal failure (OR: 13.00; 95% CI: 2.88, 58.70; N=454) or Parkinson's Disease (OR: 2.80; 95% CI: 1.24, 6.34; N=1254). However, there was no significant difference in probability of post-operative delirium for diabetes mellitus, hypertension, atrial fibrillation, COPD, cancer (undefined what type), or hearing impairment (p≥0.06; **Table 2**).

There was no significantly greater chance of experiencing post-operative delirium in people who demonstrated a CCI score of greater than three (OR: 1.92; 95% CI: 0.78, 4.69; N=120). Although there was evidence of a lower chance of post-operative delirium in those who had a ASA Grade 1 (OR: 0.25; 95% CI: 0.11, 0.58; N=722) and ASA Grade 2 (OR: 0.48; 95% CI: 0.28, 0.81; N=924), there was moderate quality evidence that those with a ASA Grade 3 (OR: 2.23; 95% CI: 1.67, 2.98; N=924), or ASA Grade 4 (OR: 2.55; 95% CI: 1.29, 5.03; N=863) were over two-times more likely to experience post-operative delirium.

There was no significant difference in probability of post-operative delirium based on fracture type (p≥0.55; **Supplementary Figure 4**) or prescription of antidepressants prior to admission (p=0.44). There was however, low quality evidence that those prescribed anti-psychotic medications were at greater chance of experiencing post-operative delirium (OR: 2.33; 95% CI: 1.22, 4.42; N=603). There was also low quality evidence that the greater the number of prescribed medications was associated with experiencing post-operative delirium (MD: 0.64; 95% CI: 0.25, 1.02; N=632).

Meta-Analysis – Intra-operative Variables

There was no significant difference in intra-operative variables between those who experienced post-operative delirium following hip fracture surgery and those who did not for the nine variables assessed (p≥0.12; **Table 3**). This included anaesthetic type, intra-operative blood loss and duration until surgery.

Meta-Analysis – Post-operative Variables

A summary of the meta-analysis findings from the post-operative variables is presented in **Table 3**. There was lower quality evidence of a nearly three-fold increase in the chance of post-operative delirium with post-operative use of morphine (OR: 2.95; 955 CI: 1.09, 8.12; N=144), but no

association between length of hospital stay and the development of post-operative delirium (MD: 0.75 days; 95% CI: -0.03, 1.53; N=985). There was moderate quality evidence to suggest those who experienced post-operative pneumonia (OR: 2.97; 95% CI: 1.06, 8.35; N=440), or a urinary tract infection (OR: 3.52; 95% CI: 1.72, 7.22; N=536) were at nearly three-times and four-times greater chance of post-operative delirium respectively. There were however no associations between post-operative stroke (p=0.20), pulmonary (p=0.54) or thromboembolic complications (p=0.72) and post-operative delirium.

DISCUSSION

The findings of this analysis suggest that whilst a number of on-admission and patient characteristics, most notably age, dementia and overall general health are indicative of the probability of experiencing delirium following hip fracture surgery, intra-operative factors do not appear to influence the prevalence of delirium based on normal clinical practice. Post-operatively, experiencing complications such as pneumonia or urinary tract infection and morphine prescription influence the probability of developing delirium. The evidence underpinning these recommendations is largely of moderate quality.

Comorbidities, as assessed using the ASA system were associated with the development of delirium. Those with an ASA Grade 3 or 4 had a two-fold increase in chance of experiencing delirium (**Table 4**). This has been previously demonstrated in patients from other surgical specialities including gastrointestinal (Scholz *et al*., 2016), spinal (Soroceanu *et al*., 2016) and colorectal (Tei *et al*., 2016). This measure of the severity of illness appears to have a clearer association with post-operative delirium compared to CCI (**Table 4**), which assesses the number of specific medical comorbidities. These findings are also seen in the literature where CCI appears less clearly associated with the incidence of delirium in an older population (Miu *et al*., 2016;

Massimo *et al*., 2016). We therefore suggest that an ASA Grade 3 or above is a stronger predictor of post-operative delirium for people with hip fracture than the CCI score.

The findings from this study indicate that there is no association between the duration from admission to surgery and post-operative delirium. This study was only able to assess overall duration and it was not possible to evaluate whether the time-point patients were at within that specific period of time affected risk. In contrast Bo et al (2016) reported that a length of stay in an emergency department of greater than 10 hours was associated with a two-fold increased probability of incident delirium in individuals aged 75 years and over. Further analyses examining the patient pathway and duration spent in the emergency department, medical/surgical assessment units, orthopaedic wards and rehabilitation would be valuable to begin to explore where interventions may be best implemented to reduce the risk of delirium during the patient's hospital admission. Similarly, it remains unclear from these data whether there is a difference in the risk of delirium between admission onto an orthogeriatric ward or a standard orthopaedic ward. This has been previously reported in one trial suggesting no difference in incident delirium rates (p=0.51)(Watne *et al.,* 2014); however, further specific exploration of the influence of this on delirium rates is warranted.

The finding that morphine use is associated with increased probability of delirium has been previously reported in non-hip fracture cohorts. Grandahl et al (2016) reported the association with delirium and morphine use in cancer care, as well as with other medications such as benzodiazepine. Despite our results indicated that those on antipsychotic medications on admission were significantly more likely to experience post-operative delirium; there was insufficient data to identify a potential association with anticholinergic medications, such as benzodiazepine. Anticholinergics have been associated with cognitive impairment (Fox *et al*., 2014), reduced functional recovery (Sakel *et al*., 2015) and increased incident delirium in non-surgical elderly cohorts (Naja *et al*., 2016). Siddiqi et al (2016) reported that there remains no clear evidence as to whether cholinesterase inhibitors or antipsychotic medications reduce

incident delirium when used peri-operatively. Further examination of whether the use of these medications prior to hip fracture can be used as an indicator for differing prognosis is important.

As Orena et al (2016) acknowledged, delirium is multifactorial in nature. Numerous variables are associated with its occurrence. This review has indicated that anaesthetic and other intra-operative variables did not have a significant association on the incidence of post-operative delirium. This is in agreement with previous surgical analyses on hip and non-hip fracture populations (Mason *et al*., 2010). However, due to the nature of the available data, it was not possible to ascertain whether factors such as depth of anaesthesia or administration of pre-operative medications immediately prior to surgery were associated with delirium incidence.

This paper presented with two limitations. Firstly it was not possible to determine when delirium was reported. We had planned to assess delirium at follow-up intervals of initial post-operatively period to Day 3 (immediate), Day 4 to Day 7 (shorter-term), and Day 8 to acute hospital discharge (longer-term). This would have been particularly valuable when interpreting variables such as morphine use as it remains unclear whether there is a time-relationship to this variable. It is not possible to ascertain from the current evidence whether morphine causes delirium, or whether pain or dyspnoea (or the underlying disease causing the pain or dyspnoea) causes delirium in relation to morphine use. More detailed reporting of the administration of pharmacological agents for this population would be valuable. As more data are reported it is anticipated that additional subgroup analyses may be undertaken to investigate this potential effect. Second, some of the outcome variables in the meta-analysis may be attributed to type II statistical error. For example, whilst a comorbidity score of greater than one (seen in N=374) was associated with delirium, a comorbidity score of greater than three (seen in N=120) showed no association. However, many of the individual diseases that contributed to the comorbidity score did show association (**Table 2**). Accordingly, as further data becomes available, it will be important to incorporate these patient data to retest the conclusions drawn from this analysis by mitigating type II error.

CONCLUSION

There is moderate quality evidence to predict the risk of post-operative delirium following hip fracture surgery based on older age, pre-existing cognitive impairment and overall general health pre-operatively. Post-operatively, experiencing pneumonia or a urinary tract infection, and receiving morphine increases the probability of incident post-operative delirium. Based on these findings, clinicians should be vigilant for delirium in their patients who present with these features on admission and following hip fracture surgery.

DECLARATIONS

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FIGURE AND TABLE LEGENDS

Figure 1: PRISMA flow-chart search strategy results.

Figure 2: Forest plot assessing probability of experiencing post-operative delirium when assessed by mean difference in age.

Table 1: Characteristics of included studies

Table 2: Results from the meta-analyses on on-admission characteristics and variables

Table 3: Results from the meta-analyses on intra-operative and post-operative variables

Supplementary Table 1: MEDLINE search strategy

Supplementary Table 2: Downs and Black quality assessment results

Supplementary Figure 1: Funnel plot assessing for the risk of small sample size publication bias.

Supplementary Figure 2: Forest plot assessing probability of experiencing post-operative delirium when assessed by when the individual lived in a care home institution on-admission.

Supplementary Figure 3: Forest plot assessing probability of experiencing post-operative delirium when assessed by presence of dementia on-admission.

Supplementary Figure 4: Forest plot assessing probability of experiencing post-operative delirium when assessed by fracture classification.

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Table 1: Characteristics of included studies

Study	Country of Origin	N	N		Mean Age (years)		Sex (female/male)		Assessment of Delirium
			Delirium	No Delirium	Delirium	No Delirium	Delirium	No Delirium	
Bitsch (2006)	Denmark	100	31	65	84.5	81.6	25/6	43/22	MMSE
Bjorkelund (2011)	Sweden	428	223	201	NR	NR	158/65	153/48	SPMSQ
Chen (2014)	China	186	70	116	80.1	74.7	50/20	89/27	CAM
Chrispal (2010)	India	81	17	64	73.7	71.3	6/11	26/38	CAM
Dolan (2000)	USA	682	92	590	83.0	80.0	71/21	466/124	CAM
Edlund (2001)	Sweden	71	19	52	80.0	78.3	49/6	10/9	MMSE, OBS
Fortes-Filho (2016)	Brazil	147	61	86	83.8	77.2	45/16	62/24	CAM
Freter (2005)	Canada	100	24	76	NR	NR	19/5	63/13	CAM
Furlaneto (2006)	Brazil	103	30	73	82.5	80.1	25/5	60/13	CAM
Galanakis (2001)	Germany	105	25	80	81.8	72.8	19/6	57/23	CAM
Goldenberg (2006)	USA	77	37	40	NR	NR	NR	NR	CAM
Guo (2016)	China	572	452	120	82.0	76.0	36/84	170/282	CAM
Ilango 2016)	Australia	318	172	146	84.2	78.7	52/120	37/109	PAS, VPS, PADS
Juliebø (2009)	Norway	187	68	119	85.0	82.0	55/13	90/29	CAM
Kalisvaart (2006)	Netherlands	603	74	529	81.8	77.4	53/21	412/117	CAM
Lee (2011)	South Korea	232	70	162	80.3	78.5	49/21	124/38	CAM
Luger (2014)	Austria	329	18	259	87.9	88.4	13/5	225/34	DSM-4

Liu (2014)	China	217	38	179	NR	NR	NR	NR	NR
Marcantonio (2000)	USA	126	52	74	NR	NR	42/10	57/17	CAM
Meziere (2013)	France	52	7	45	88.3	83.8	7/0	30/15	CAM
Morrison (2003)	USA	541	86	455	ND	ND	65/21	377/78	CAM
Nie (2012)	China	123	16	107	75.0	75.3	12/4	73/34	CAM, DRS-R-98
Papadopoulos (2012)	Greece	69	18	51	76.7	73.6	NR	NR	MMSE
Radinovic (2014)	Serbia	187	88	99	73.7	75.0	64/24	74/25	CAM
Santana Santos (2005)	Sweden	34	19	15	82.9	81.5	13/6	12/3	CAM
Schuurmans (2003)	Netherlands	92	18	74	82.6	82.2	16/2	64/10	DOS
Shen (2013)	China	458	68	390	75.9	69.4	42/26	241/149	NR
Wang (2015)	USA	103	23	80	84.0	81.0	15/8	58/22	CAM
Wang (2008)	China	91	32	36	NR	NR	NR	NR	CAM
Watne (2014)	Norway and Scotland	148	72	72	NR	NR	51/21	56/16	CAM, MDAS, DRS-R-98
Westhoff (2013)	Netherlands	62	23	38	84.6	82.9	16/7	26/12	CAM, DRS-R-98
Zakriya (2002)	USA	168	47	121	79.0	77.0	28/19	93/28	CAM

CAM - Confusion Assessment Method; DOS – Delirium Observation Screening; DRS-R-98 – Delirium Rating Scale-Revised-98; DSM-4 – Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); MDAS – Memorial Delirium Assessment Scale; MMSE – Mini Mental State Examination; Organic Brain Syndrome; NR- Not Reported; PADS - Pain assessment in Advanced Dementia Scale; PAS - Pittsburgh Agitation Scale; SPMSQ – Short Portable Mental Status Questionnaire; VPS - Verbal Pain Scale

Table 2: Results from the meta-analyses on on-admission characteristics and variables

Variable	N (Study Number)	OR (95% CI)	P-value	Statistical Heterogeneity		GRADE Assessment
				I^2 (%)	Chi^2	
Demographics						
Male Sex	6279 (29)	1.13 (0.99, 1.30)	0.07	4	0.41	Moderate
Female Sex	6277 (29)	0.88 (0.77, 1.01)	0.07	11	0.30	Moderate
Mean Age	4071 (20)	2.91 (1.89, 3.93)*	<0.001	81	<0.001	Moderate
Aged ≥80 years	394 (4)	1.77 (1.09, 2.87)	0.02	0	0.94	Low
Institutional home resident	2257 (11)	2.65 (1.79, 3.92)	<0.001	52	0.02	Moderate
Smoker	560 (4)	1.62 (0.60, 4.34)	0.34	50	0.11	Low
BMI	1093 (4)	-0.26 (-0.58, 0.06)*	0.12	0	0.55	Low
MMSE	1275 (8)	-3.52 (-4.07, -0.73)*	0.002	93	<0.001	Moderate
MMSE < 24	260 (3)	3.44 (1.78, 6.66)	<0.001	0	0.86	Low
Fracture classification						
Cervical fracture	1747 (9)	1.07 (0.84, 1.34)	0.59	14	0.32	Moderate
Intertrochanteric fracture	1747 (9)	1.01 (0.74, 1.36)	0.96	33	0.16	Moderate
Subtrochanteric fracture	458 (3)	0.59 (0.10, 3.36)	0.55	43	0.18	Low
Medical comorbidities						
Diabetes Mellitus	1488 (6)	0.91 (0.39, 2.09)	0.82	73	0.002	Moderate
Hypertension	1316 (6)	1.18 (0.88, 1.58)	0.27	20	0.28	Low
Cardiac failure	2120 (7)	3.23 (1.84, 5.66)	<0.001	70	0.003	Moderate
Atrial Fibrillation	1348 (4)	3.64 (0.97, 13.71)	0.06	81	0.001	Low
Renal Failure	454 (3)	13.00 (2.88, 58.70)	<0.001	49	0.14	Low
Dementia	2355 (12)	6.07 (4.84, 7.62)	<0.001	25	0.20	Moderate
COPD	1579 (6)	1.34 (0.56, 3.19)	0.51	75	0.001	Low
Cancer	1055 (3)	0.84 (0.19, 3.79)	0.82	78	0.01	Low
Depression	905 (5)	2.61 (1.07, 6.34)	0.03	51	0.09	Moderate
Stroke	2036 (5)	3.55 (1.56, 8.07)	0.002	84	<0.001	Moderate
Parkinson's Disease	1254 (2)	2.80 (1.24, 6.34)	0.01	0	0.73	Low
Hearing impairment	249 (3)	1.08 (0.17, 6.80)	0.93	80	0.006	Low
Visual impairment	1179 (7)	2.03 (1.02, 4.04)	0.04	61	0.02	Moderate

Charlson Comorbidity Index	394 (3)	0.33 (0.03, 0.64)*	0.03	0	0.63	Low
Charlson Comorbidity Index >3	120 (2)	1.92 (0.78, 4.69)	0.15	0	0.43	Low
Charlson Comorbidity Index >1	374 (2)	1.62 (0.95, 2.78)	0.08	32	0.23	Low
Mean number of comorbid conditions	1109 (4)	0.50 (0.23, 0.77)*	<0.001	21	0.29	Moderate
ASA Grade 1	722 (5)	0.25 (0.11, 0.58)	0.001	0	0.94	Low
ASA Grade 2	924 (7)	0.48 (0.28, 0.81)	0.006	63	0.01	Moderate
ASA Grade 3	924 (7)	2.23 (1.67, 2.98)	<0.001	0	0.49	Moderate
ASA Grade 4	863 (6)	2.55 (1.29, 5.03)	0.007	0	0.93	Moderate
Medication						
Mean number of prescribed medications	632 (5)	0.64 (0.25, 1.02)*	0.001	0	0.61	Low
Prescribed antidepressants	280 (3)	1.63 (0.48, 5.55)	0.44	36	0.21	Low
Prescribed anti-psychotics	603 (5)	2.33 (1.22, 4.42)	0.01	0	0.71	Low

* Mean difference effect estimate; ASA – American Society for Anesthesiologists score; BMI – body mass index; CI – confidence intervals; COPD – chronic obstructive pulmonary disease; I2 – inconsistency value; MMSE – Mini Mental State Examination; OR – odd ratio; P-value – probability value;

Table 3: Results from the meta-analyses on intra-operative and post-operative variables

Variable	N (Study Number)	OR (95% CI)	P-value	Statistical Heterogeneity		GRADE Assessment
				I^2 (%)	Chi^2	
Intra-operative Variables						
Days until surgery (days)	1281 (5)	0.31 (-0.31, 0.92)*	0.33	40	0.16	Moderate
Time until surgery (hours)	311 (2)	-0.05 (-0.52, 0.43)*	0.84	28	0.24	Low
Regional Anaesthetic	1101 (4)	1.27 (0.91, 1.77)	0.15	17	0.31	Moderate
General Anaesthetic	1864 (9)	1.00 (0.59, 1.69)	1.00	69	0.001	Low
Spinal Anaesthetic	697 (4)	1.44 (0.91, 2.26)	0.12	0	0.66	Moderate
Mean duration of anaesthetic	658 (5)	-0.36 (-4.70, 3.98)*	0.87	18	0.30	Low
Requirement for blood transfusion	809 (3)	1.92 (0.83, 4.45)	0.13	72	0.03	Low
Mean intra-operative blood loss	1187 (4)	26.17 (-52.39, 104.73)*	0.51	94	<0.001	Low
Amount of fluid transfused	418 (2)	6.78 (-25.68, 39.24)*	0.68	0	0.75	Low
Post-operative Variables						
Length of hospital stay (days)	985 (8)	0.75 (-0.03, 1.53)*	0.06	24	0.23	Moderate
Post-operative morphine use	144 (2)	2.98 (1.09, 8.12)	0.03	0	0.51	Low
Pneumonia	440 (3)	2.97 (1.06, 8.35)	0.04	12	0.32	Moderate
Urinary tract infection	536 (4)	3.52 (1.72, 7.22)	<0.001	0	0.42	Moderate
Stroke	373 (2)	3.82 (0.50, 29.44)	0.20	40	0.20	Low
Pulmonary complication	373 (2)	1.46 (0.44, 4.79)	0.54	45	0.18	Low
Thromboembolic complications	373 (2)	0.71 (0.12, 4.38)	0.72	0	0.37	Moderate

* Mean difference effect estimate; CI – confidence intervals; I^2 – inconsistency value; OR – odd ratio

Supplementary Table 1: MEDLINE search strategy

1. hip/ or hip joint/ or hip.ti,ab.
2. exp Hip Fracture/
3. ((hip* or femur* or femoral* or trochant* or pertrochant* or intertrochant* or subtrochant* or intracapsular* or extracapsular*) adj4 fracture*).ti,ab.
4. OR/1-3
5. (pin* or nail* or screw* or plate* or arthroplast* or fix* or prosthes*).ti,ab.
6. Internal Fixators/ or Bone Screws/ or Fracture Fixation, Internal/ or Bone Plates/ or Bone Nails/
7. exp Arthroplasty/ Or Arthroplasty, Replacement, Hip/
8. OR/5-7
9. exp Delirium/
10. Deliri*.ti,ab.
11. Confus*.ti,ab.
12. POCD.ti,ab.
13. post-operative cognitive disorder.ti,ab.
14. acute confusional state.ti,ab.
15. OR/9-14
16. exp Pre-operative care/ or Pre-operative Period/
17. exp Perioperative care/ or Perioperative Period/
18. exp Intraoperative care/ or Intraoperative Period/
19. exp Anesthetics, genderal/ or Anesthetics, local anaesthet* adj2 (regional block or spinal).ti.ab
20. OR/16-19
21. exp Complications/
22. exp. Morbidity/
23. exp Blood loss, surgical/
24. blood transfus*.ti.ab.
25. exp Length of stay/
26. exp Diabetes mellitus/
27. exp Hypertension/
28. exp Arrhythmias, Cardiac/ or atrial fibrillation/ or Heart arrest/ or Heart Diseases/ or Heart Failure/
29. exp Renal insufficiency/
30. exp Dementia/
31. exp/ Pulmonary Disease, Chronic Obstructive/
32. COPD.ti,ab.
33. exp Neoplasms/
34. Cancer or tumors.ti,ab.
35. exp Depression/
36. exp Stroke/
37. cerebrovascular accident or CVA or vascular accident.ti.ab.
38. deep vein thromb* or DVT or pulmonary embol* or PE or thromboembol* or thrombos*.ti.ab.
39. OR/21-38
40. AND/4,8,15,20,39

Supplementary Table 2: Downs and Black quality assessment results

	Reporting										External Validity			Internal validity (bias)							Internal validity (selection)						Power
Criteria/Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Bitsch (2006)	1	1	1	0	1	1	1	1	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	0	0
Bjorkelund (2011)	1	1	0	0	1	1	1	0	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	1	1	0
Chen (2014)	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Chrispal (2010)	1	1	1	1	2	1	0	1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Dolan (2000)	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Edlund (2001)	1	1	0	1	0	1	1	0	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Fortes-Filho (2016)	1	1	1	0	0	1	1	0	0	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Freter (2005)	1	1	0	0	0	1	1	0	1	0	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	1	0
Furlaneto (2006)	1	1	0	0	0	1	1	0	1	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	1	0
Galanakis (2001)	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Goldenberg (2006)	1	0	0	0	0	0	0	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	0	0
Guo (2016)	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	0	0	1	0	1	1	1	0	0	0	1	0
Ilango 2016)	1	1	1	1	2	1	1	1	1	1	1	1	1	0	0	0	1	0	1	1	1	1	0	0	0	0	0
Juliebø (2009)	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Kalisvaart (2006)	1	1	1	0	1	1	1	0	1	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	1	0
Lee (2011)	1	1	1	1	2	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Luger (2014)	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0

Liu (2014)	1	1	0	0	1	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Marcantonio (2000)	1	1	1	0	0	0	1	1	1	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	0	1	0
Meziere (2013)	1	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	1	1	0
Morrison (2003)	1	1	1	0	2	1	1	1	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Nie (2012)	1	1	0	0	0	1	1	0	1	1	1	1	1	0	0	0	1	1	0	1	1	1	0	0	0	1	0
Papadopoulos (2012)	1	1	0	0	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Radinovic (2014)	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	0	1	0	1	1	1	0	0	1	1	0
Santana Santos (2005)	1	1	1	0	1	1	1	0	1	1	1	0	1	O	0	1	1	1	0	1	1	1	0	0	1	1	0
Schuurmans (2003)	1	1	1	0	2	1	1	1	1	1	0	0	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Shen (2013)	1	1	1	0	0	1	1	0	1	1	0	0	0	0	0	1	1	0	0	1	1	1	0	0	0	1	0
Wang (2015)	1	1	1	0	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	1	1	0
Wang (2008)	1	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	1	1	1	1	1	1	0	0	0	0	0
Watne (2014)	1	1	0	1	0	1	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0
Westhoff (2013)	1	1	1	1	1	1	1	1	0	0	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	0	0
Zakriya (2002)	1	1	1	0	0	0	1	0	1	1	1	1	1	0	0	1	1	1	0	1	1	1	0	0	0	1	0

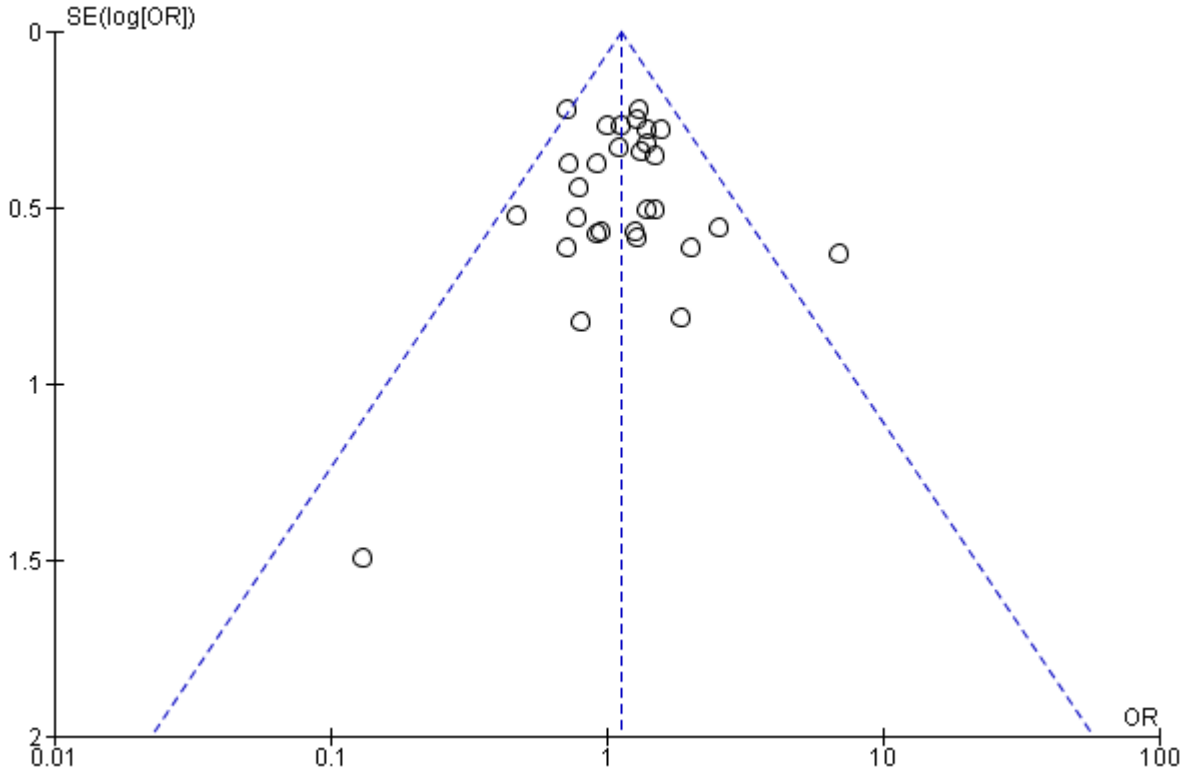
NA – Not applicable; T – Total

Critical Appraisal Items:

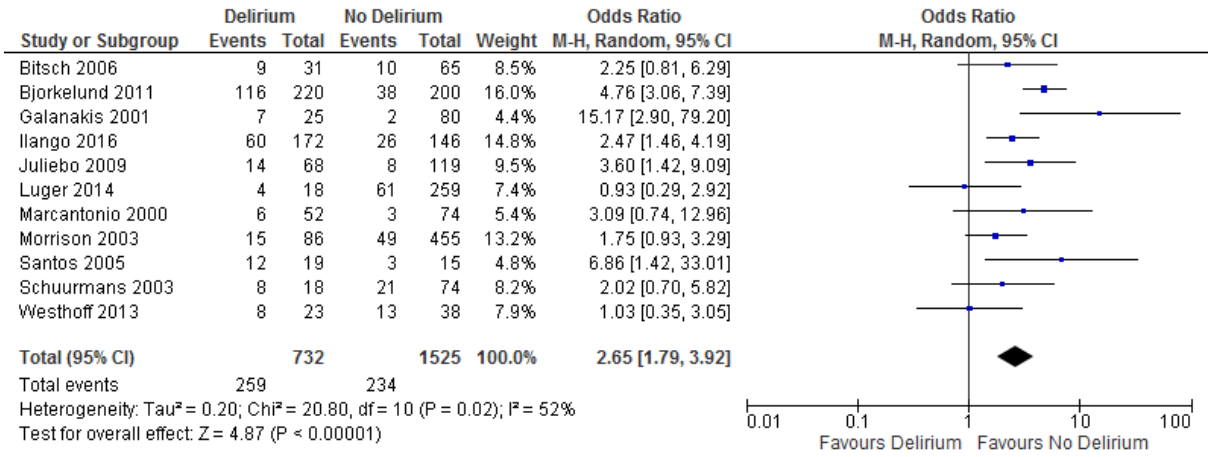
1. Is the hypothesis/aim/objective of the study clearly described?
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?
3. Are the characteristics of the patients included in the study clearly described?
4. Are the interventions of interest clearly described?

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?
6. Are the main findings of the study clearly described?
7. Does the study provide estimates of the random variability in the data for the main outcomes?
8. Have all important adverse events that may be a consequence of the intervention been reported?
9. Have the characteristic of patients lost to follow-up been described?
10. Have actual probability values been reported (e.g. 0,035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?
13. Were the staff, places and facilitates where the patients were treated, representative of the treatment the majority of patients received?
14. Was an attempt made to blind study subjects to the intervention they have received?
15. Was an attempt made to blind those measuring the main outcomes of the intervention?
16. If any of the results of the study were based on "data dreading" was this made clear?
17. In trials and cohort studies, were the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?
18. Were the statistical tests used to assess the main outcome appropriate?
19. Was compliance with the intervention/s reliable?
20. Were the main outcome measures used accurate (valid and reliable)?
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time?
23. Were study subjects randomized to intervention groups?
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
26. Were losses of patients to follow-up taken into account?
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance <5%

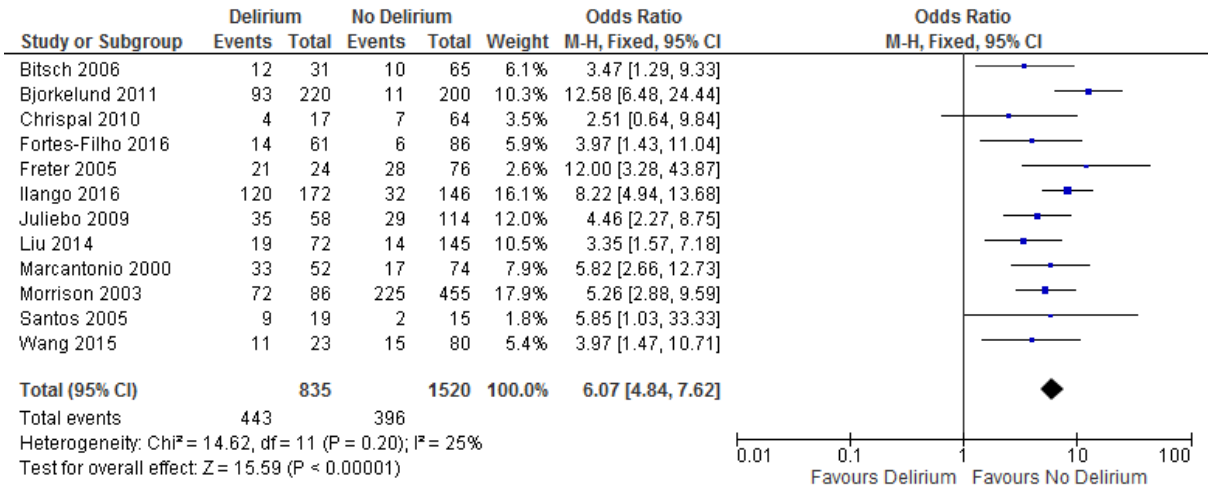
Supplementary Figure 1: Funnel plot assessing for the risk of small sample size publication bias.



Supplementary Figure 2: Forest plot assessing probability of experiencing post-operative delirium when assessed by when the individual lived in a care home institution on-admission.



Supplementary Figure 3: Forest plot assessing probability of experiencing post-operative delirium when assessed by presence of dementia on-admission.



Supplementary Figure 4: Forest plot assessing probability of experiencing post-operative delirium when assessed by fracture classification.