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The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Title Page

The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Abstract

Background
Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium.

Objective
This systematic review will investigate the impact of anaesthetic technique on post-operative delirium. Other outcomes included mortality, length of stay, complications and functional outcomes.

Design
Systematic review of randomised controlled trials and non-randomised controlled studies

Data Sources
Bibliographic databases were searched from inception to October 2016. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers were searched to identify on-going trials.

Eligibility criteria
Studies were eligible if general and regional anaesthesia were compared in patients (aged 60 and over) undergoing hip fracture surgery, reporting primary outcome of post-operative delirium and secondary outcomes of mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life. Exclusion criteria were anaesthetic technique or drug not considered current standard practice; patients undergoing hip fracture surgery alongside other surgery and uncontrolled studies.

Results
Eighty-nine studies were included. There was no evidence to suggest that anaesthesia type influences post-operative delirium or mortality. Some studies suggested a small reduction in length of hospital stay with regional anaesthesia. There was some evidence to suggest that respiratory complications and intraoperative hypotension were more common with general anaesthesia. Heterogeneity precluded meta-analysis. All findings were described narratively and data were presented where possible in forest plots for illustrative purposes.

Conclusions

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodological rigorous study.

This review is registered with PROSPERO (CRD42015020166).
Strengths and limitations of this study

• This systematic review provides an update to evidence that examines whether the type of anaesthesia affect the development of post-operative delirium in patients with hip fractures.

• The review included randomised and non-randomised studies that included one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.

• Other outcomes were mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
**Introduction**

There are an estimated 70,000-75,000 hip fractures in the UK each year with an annual cost of £2 billion. [1] This is projected to rise and reach 100,000 patients a year and costing £3.6-5.6 billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current illness [3] and are at risk of mortality and significant morbidity. In 2014, the National Hip Fracture Database reported 30-day mortality as 7.5%. [4] Following surgery, adverse outcomes can include delirium, myocardial infarction, pneumonia, and cerebrovascular accident. [5]

Delirium is a common neuropsychiatric syndrome defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as the disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day. [6,7] Post-operative delirium has been reported to affect between 32%-53.3% of patients and is associated with prolonged hospital stay, discharge to care homes, difficulty in regaining function in activities of daily living and increased risk of development of cognitive dysfunction and dementia in the future. [8–12] [13] The aetiology of delirium is multifactorial, with both modifiable and non-modifiable risk factors. [14,15] There is no known treatment for delirium, however careful approach in the peri-operative period may reduce its incidence and severity. [6,9,15–18] Guideline committees have cautiously recommended that regional anaesthesia should be given unless contraindicated. [1,9,19] Despite this, the type of anaesthesia administered in patients with hip fractures remains varied. [4]

Ninety-eight percent of patients with hip fracture are offered surgery and will require anaesthesia. [5] Anaesthesia can be broadly classified into general (GA) or regional anaesthesia (RA). RA uses neuraxial blocks that avoid the use of GA drugs and opiates which have been linked to post-operative delirium. [3] Excessive depth of anaesthesia and perioperative hypotension has been reported in GA patients and are both...
associated with an increased risk of mortality. [20] However, the risk of perioperative hypotension and sedation is not completely eradicated with RA. [21,22]

Findings from previous systematic reviews looking at the effects of type of anaesthesia on post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,25,26] and reduced incidence of post-operative delirium in patients having RA. [3,5,22–24] However some studies included in these reviews reported use of out-dated anaesthetic drugs that are no longer relevant to current clinical practice. [5,26] Further limitations were the inclusion of only randomised controlled trials, [3,5,25,26] lack of focus on delirium as a primary outcome, [3,5,22,24,26] a limited search strategy [22] and restrictive selection criteria (e.g. exclusion of studies with patients with cognitive impairment). [23–25] Inadequate exploration of heterogeneity relating to delirium assessment and rating scales and assessment time points was also common. This systematic review aims to provide an up-to-date, comprehensive and methodologically robust analysis to examine the effect of RA versus GA on post-operative delirium and other outcomes in older patients undergoing surgery for hip fracture.

**Methods**

The protocol for this systematic review has been published and is registered with PROSPERO (CRD42015020166). [27] A summary of the methods is outlined below. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [28]

**Search strategy and selection criteria**

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to October 2016 using a combination of index terms and key words relating to the population, intervention and comparator and outcomes (see Appendix A for sample search strategy). There was no restriction by search date, study design or language. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked,
and clinical trial registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

**Study selection**

Studies were eligible for inclusion if they met the following pre-defined criteria:

1) Population - patients aged ≥60 years (or with a majority ≥60) undergoing surgery for fragility hip fracture.

2) Intervention and comparator – one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK. [19]

3) Outcomes – primary outcome: post-operative delirium (any criteria as defined by study authors); secondary outcomes: mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.

4) Randomised or non-randomised controlled studies (prospective or retrospective).

Exclusion criteria were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthetis agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and uncontrolled studies. Reasons for exclusion were recorded at the full text stage.

**Data Extraction and Quality Assessment**

A piloted, standardised data extraction form was used to record information on study design, patient characteristics, type of surgery, anaesthesia type, and outcomes. The Cochrane Collaboration risk of bias tool [29] was used to assess the methodological quality of randomised controlled trials and the Newcastle-Ottawa scale [30] for non-randomised studies. Full translations could not be obtained for three included studies [31–33], extracted data is therefore based mainly on numerical data and the English abstract.
Data analysis and synthesis

Findings were grouped according to outcome. Where there was sufficient data, results were presented in forest plots (delirium, mortality and length of hospital stay). Effect estimates were not pooled as clinical and methodological heterogeneity was considered to be too great. Forest plots were thus used for illustrative purposes only and potential sources of heterogeneity (such as study design or timing of assessment) have been highlighted. Adverse events were tabulated, where possible, according to the post-operative morbidity survey (POMS) criteria. [34] Findings for other outcomes (functional outcomes, quality of life, discharge location) were reported narratively as heterogeneity and/or a paucity of data precluded representation in forest plots. Formal sensitivity analysis according to study quality, and assessment of publication bias using funnel plots were not possible.

Results

Of 4223 citations screened, 89 studies met the eligibility criteria (Figure 1). There were 5 randomised controlled trials (RCTs), 28 prospective and 56 retrospective controlled studies.

Eighteen studies reported delirium (4 RCTs, [35–38] 7 prospective [18,39–44] and 7 retrospective studies [45–51]; 51 studies reported mortality (2 RCTs, [35,38] 10 prospective [41,44,52–59] and 38 retrospective studies [4,20,21,31,32,45,48,49,51,60–88]); 21 studies reported length of hospital stay (2 RCTs, [36,38] 5 prospective, [41,44,54,89,90] and 14 retrospective studies [21,48,53,62,64,65,69,72,74–77,91,92]); 25 studies reported adverse events (3 RCTs [35,36,93] 7 prospective [41,42,44,54,89,94,95] and 15 retrospective studies [20,21,45,48,49,62,63,65,69,73–75,91,96,97]); 8 studies reported functional outcome (2 RCTs, [35,36] 3 prospective [41,44,98] and 3 retrospective studies [58,67,99]) and 3 studies reported discharge location (1 prospective [42] and 2 retrospective studies [21,45]).
Ten potentially relevant ongoing trials were identified, with two (NCT02190903 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

**Study, population and intervention characteristics**

Given the large number of studies identified, only the 18 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

**Primary Outcome**

**Post-operative delirium**

Fourteen studies are represented in the forest plot (Figure 2), including three of the four RCTs. Based on these 14 studies, there is no evidence of a benefit of one type of anaesthesia over another. Four further studies not represented in the forest plot (one RCT, [35] two retrospective analyses reported as abstracts only, [47,50] and one prospective study [31]), also found no significant differences in delirium based on Abbreviated Mental Test (AMT) or DSM-IV.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the assessment tools used [38] and method of randomisation. [35,36,38] Blinding of outcome assessment was either not undertaken [38] or unclear, [36] with only one RCT having a clear statement on blinding. [35] There appeared to be no loss to follow-up in two RCTs [36,38], but this was unclear for the other RCT. [35] The RCT by Kamitani was not quality assessed as a full translation was not available. [37]

The observational studies were generally considered to be at low risk of bias in terms of patient eligibility, however most had no details on blinding of outcome assessors and the level of completeness of data was not well described (Table 2b). There were no details on characteristics of completers compared with those lost to follow up. There was also a lack of detail on the type of assessment tool used and/or where the cut-off for a “positive” diagnosis of delirium was.
Most studies did not adjust for potential confounders, but four studies [31,41,49,50], one of which is also represented in the above plot [49], did present adjusted results (Figure 2). There was some variation in terms of which confounders were adjusted for. None found that type of anaesthesia was predictive of post-operative delirium.

There was substantial heterogeneity across the 18 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 6 out of 18 studies used either DSM-IV criteria [18,46,50,51] or AMT. [35,47] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

**Secondary outcomes**

**Mortality**

Two RCTs and 9 studies reported adjusted mortality (Figure 3, supplementary data). Most studies found no statistically significant differences between types of anaesthesia. One RCT found a small and statistically significant mortality benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Two further studies[41,73] reporting adjusted results did not find statistically significant results favouring either type of anaesthesia. Where studies reported both adjusted and unadjusted results, it is notable that in some cases the direction of effect or statistical significance changes; this emphasises the fact that unadjusted results should be interpreted very cautiously. Furthermore, there was a lack of reporting and consistency in terms of which variables were adjusted for.

Of the remaining 38 studies reporting unadjusted mortality results only, six [52,56,61,67,68,70] found statistically significant results in favour of RA. The remainder found no statistically significant differences and no consistent trend of benefit.
Overall there is a paucity of good quality evidence evaluating mortality, with only one good quality RCT [38] suggesting benefit from GA at later, but not earlier time points.

Length of hospital stay

Twenty-one [21,36,38,41,44,48,53,54,62,64,65,69,72,74–77,89–92] studies reported length of hospital stay; nine could be included in a forest plot (Figure 4, supplementary data). There was no difference in length of hospital stay based on one RCT. [38] The adjusted results, based on three retrospective studies, [21,62,75] showed a slight trend towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,62] the absolute reduction was small (up to around a third of a day). Results from the studies reporting unadjusted results were inconsistent, with three finding no difference, [65,69,74] and two finding a benefit from RA. [76,89]

Of the remaining twelve studies [36,41,44,48,53,54,64,72,77,90,91,100], neither the RCT [36] nor the four prospective studies [41,44,54,90] showed any significant differences. Results from the seven retrospective studies were also inconsistent (three studies [53,64,77] reported no difference, two studies [48,72] found a statistically significant benefit for RA [72] and one [91] a statistically significant benefit for GA.)

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of ten studies [21,36,44,48,53,64,65,77,90,91] reporting the median, eight studies [21,36,44,53,64,65,77,90] found no statistically significant differences. Two studies found a statistically significant difference in medians favouring RA [48] or GA [91] respectively.

Adverse Events

Twenty-five studies reported adverse events (Table 3, supplementary data). There were many gaps in reporting of POMS adverse events, and it is uncertain whether this reflects non-occurrence or non-reporting of such events. Most commonly reported adverse events were pulmonary (10 studies) [20,21,35,45,48,49,62,69,89,91] and cardiovascular events (8 studies). [21,35,45,54,62,63,75,91] For pulmonary events, six
studies found no statistically significant differences. [35,45,49,69,89,91] Four studies found a statistically significant difference in favour of RA (fewer cases of ventilatory support [62], respiratory failure [20,62] and ‘overall pulmonary’ adverse events [20,48]). There were no differences in occurrences of pneumonia [35,45,49,91] or hypoxia. [69,89] The most commonly reported cardiovascular adverse events were myocardial infarction [45,62,91] and thromboembolic events. [35,54,63,75,91] No differences were found for myocardial infarction. [45,49,62,69,91] Three studies [63,75,91] reported higher incidence of thromboembolic events in GA group.

Nine studies summarised overall adverse events with the majority finding no differences between the types of anaesthesia. Where there was a significant difference, this was in favour in RA (e.g. fewer incidences of ‘all complications’, [48,63] ITU admissions, [62] stroke [62] or requirement for blood transfusion). Three studies [93,95,97] found higher incidences of hypotension in the GA group.

The results are thus suggestive of a lower incidence of post-operative respiratory, cardiac and overall complications in the RA group. However, reporting of adverse events, including methods of ascertainment, was inconsistent and limited.

**Functional outcomes**

Eight studies reported functional outcomes using a variety of outcome measures. A small RCT reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] A further RCT [36] reported a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005). No differences were found in the non-randomised studies regarding time to ambulation, [98,99] walking speed, [58] time to rise from chair, [41] mean Barthel’s score [67] or ambulation at 3, 6 and 12 month post-surgery. [44] Overall results may suggest a small benefit from RA for immediate post-anaesthetic mobilisation. However, the evidence is limited by small sample size, unknown method of outcome assessment and blinding of assessors.

**Discharge location**
Three non-randomised studies described discharge locations of patients following hip fracture. [21,42,45] One study with only 14 patients reported that more patients returned home in RA group [45]. However, two larger studies [21,42] found no difference in discharge location between GA or RA group.

Quality of Life

There were no studies that evaluated the effect of type of anaesthesia on quality of life in patients after hip fracture surgery.

Discussion

For the primary outcome of post-operative delirium, this systematic review did not find any difference between types of anaesthesia. Furthermore, no survival benefit could be demonstrated with either type of anaesthesia up to one year post-operatively. A small number of studies suggested that fewer adverse events might be associated with RA. Similarly some studies were suggestive of a small reduction in hospital stay with RA. Data was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. There were no studies that reported on quality of life after different types of anaesthesia.

This is the most comprehensive and methodologically robust systematic review to date. It includes both RCTs and non-randomised controlled studies, focusing on delirium as a primary outcome as well as synthesising findings for a range of other important outcomes including adverse events. A sensitive search strategy means it is unlikely that many studies would have been missed. Careful consideration of heterogeneity has meant that no meta-analyses were undertaken, but results were presented in forest plots where possible to show the overall direction of effect and heterogeneity between studies.
Delirium can be diagnosed using the criteria from the DSM-V or the WHO’s ICD-10 classification of diseases. [7,101] However in clinical practice the criteria can be difficult to apply [102] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [103] or 4AT have been advocated as validated screening tools. (4 ‘A’s’ Test) [6,102,104] No consensus exists in the literature as to which tool should be the gold standard. [6,105,106] The accurate assessment of delirium can be affected by the presence of pain and residual drugs in the immediate period following surgery therefore timing of assessment is also important. [107] No significant differences were found for the incidence of post-operative delirium, based on four RCTs and 14 non-randomised studies but there were significant differences in the assessment tools and the assessment time-points. Most of the RCTs were small and most likely underpowered. In the largest RCT [38] delirium was not a primary outcome and the assessment tool used or the timing of assessments was not reported. The pathophysiology of delirium remains poorly understood but there are a combination of pre-existing and precipitating factors that can pre-dispose the patient to post-operative delirium. [11,108,109] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [110,111] are associated with higher risk of delirium. Precipitating factors can include acute injury such as a hip fracture, malnutrition, electrolyte imbalance and the use of urinary catheter and physical restraints. [111] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [112,113] The studies that adjusted for confounders and reported delirium [31,41,49,50] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for were demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. [41,49,50] However, with multifactorial risk factors for delirium, it is difficult to encompass all variables. Other important characteristics such as anaemia, time to surgery, blood loss, intra-operative hypotension and sedation, can also influence outcome.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total evidence included for the primary outcome)
and many of the non-randomised studies did not make any attempts to adjust for potential confounding factors. When confounding variables were considered, this was often done for mortality only. There was significant heterogeneity across studies in study design, population age, comparators, assessment time-points and definition of outcomes (particularly delirium) that precluded quantitative pooling.

Detailed reporting of anaesthetic techniques was suboptimal especially for GA technique. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium [3,114] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst most studies planned to collect adverse events data, it was unclear whether adverse events were predetermined. Small sample sizes (n<30) and rare occurrences of adverse events means that many studies were likely underpowered. [35,36,45,89]. The style of data reporting in included studies could also lead to over-reporting of complications; for example, a patient could develop pneumonia, which led to respiratory failure and the need for inotropic and ventilatory support and ITU admission. Thus five adverse events would be attributable to a single patient, but this may not be evident from the data. Incidence of intraoperative hypotension was not captured by POM categories, as inotropic support use was not reported. Hypotension can lead to hypoperfusion and organ damage. A recent analysis of data from sprint audit of outcomes in hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [93,95,97] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [49,63,93,97] also found significantly higher volumes of fluids and blood products transfused in the GA group.

Subgroup analysis was not feasible and no individual studies reported findings for different sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to GA that have not been captured by the evidence presented in this systematic review. Subgroup analysis of specific at risk patients, for example the frail and the very elderly, may suggest a benefit for either regional or general anaesthesia in certain population groups.
Older patients are at high risk of adverse outcomes post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [115] Principles of care for the older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [116] Given the lack of standardised assessment tools of delirium and the paucity of suitably powered, methodologically sound studies, uncertainty remains regarding any potential benefits of certain types of anaesthesia. However, even a modest reduction in adverse events and length of hospital stay could benefit many patients and result in cost savings for health care providers. Future research examining post-operative delirium should include robust assessment and diagnosis of delirium. There is also an urgent need for high quality research comparing anaesthetic techniques that focus on patient-related outcomes such as quality of life and functional outcomes.

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Data sharing statement: There are no unpublished data from this review.
## Table 1: Table of characteristics of studies that measured postoperative delirium

| Author Year Country | ASA | Comparison and number of patients | Population | Age, mean age and M/F split | Outcomes measured |
|---------------------|-----|-----------------------------------|------------|-----------------------------|-------------------|
| RCTs                |     |                                   |            |                             |                   |
| Bigler 1985 DENMARK|     | General: ASA 1: 2 Spinal: ASA 1: 2| Patients having acute surgery for hip fracture | Patients above 60 years of age | Postoperative mental function |
|                     |     | General (n=20) v Spinal (n=20)    | Patients undergoing hip fracture repair         | General: 77.6 years (SEM 2.3) Spinal: 80.1 years (SEM 1.6) M/F: 7/13 | -Morbidity        |
| Casati 2003 ITALY   |     | General: ASA 2: 7 Spinal: ASA 3: 8| Patients undergoing hip fracture repair         | Patients over 65 years of age | Hypotension       |
|                     |     | General (n=15) v Spinal (n=15)    | Patients undergoing hip fracture repair         | General: 84 years (67-88) | -Cognitive dysfunction |
| Study | Country | GA/Spinal Groups | GA Patient Characteristics | Spinal Patient Characteristics |
|-------|---------|------------------|---------------------------|-------------------------------|
| Kamitani 2003 | JAPAN | General (n=21) v Spinal (n=19) | Patients with femoral neck fracture | Patients aged 70 and over |
| | | | | Mean age |
| | | | | General: 81.4±6.2 |
| | | | | Spinal: 83.6±6.0 |
| | | | | M/F: 4/36 |
| Parker & Griffiths 2015 | UK | General (n=164) v Spinal (n=158) | Patients with acute hip fracture | Patients over 49 years of age |
| | | | | Mean age |
| | | | | General: 83.0 years (59-99) |
| | | | | Spinal: 82.9 years (52-105) |
| | | | | M/F: 87/235 |
### PROSPECTIVE STUDIES

| Study            | Country         | Design                          | Comparison                          | Population Description | Outcome Measures                                      |
|------------------|-----------------|---------------------------------|-------------------------------------|------------------------|--------------------------------------------------------|
| Atay 2012        | TURKEY          | General (n=30) v Spinal (n=40)   | Patients with hip fractures         | Patients aged 60 years and over | - Postoperative delirium - Postoperative cognitive function |
|                  |                 |                                 |                                      | Mean age               |                                                        |
|                  |                 |                                 |                                      | M/F:                   |                                                        |
| Bitsch 2006      | DENMARK         | ASA 1=2, ASA 2=33, ASA 3=51,    | General (n=13) v Regional (n=83)    | Hip fracture patients  | - Risk factors for pre, intra and post operative cognitive dysfunction |
|                  |                 | ASA 4=10                        |                                      | No age restriction     |                                                        |
| Bjorkelund 2010  | SWEDEN          | Intervention group (new care plan): ASA 1=17 | General (n=89) v Spinal (n=174) | Patients with hip fractures | Patients aged 65 years and over - Incidence of Delirium |
| Gilbert 2000 USA |
|------------------|
| ASA 2=59 |
| ASA 3=48 |
| ASA 4=7 |
| Control group (existing care plan: |
| ASA 1=10 |
| ASA 2=77 |
| ASA 3=42 |
| ASA 4=3 |
| General (n=311) v Spinal (n=430) |
| Patients with an acute hip fracture |
| Age 65 years and older |
| Age |
| General: |
| 65-79 years n=120 |
| 80+ years n=191 |
| Intervention: 81.1 years (SD 7.5) |
| Control: 82.0 years (SD 7.6) |
| M/F: 78/185 |
| Complications (in-hospital and surgical) |
| Functioning (daily, social, mental) |
| Study          | Country   | ASA | General (n) vs Spinal (n) | Age specified within inclusion criteria | Mean age General (SD) | Mean age Spinal (SD) | M/F | Primary | Secondary |
|---------------|-----------|-----|---------------------------|-----------------------------------------|-----------------------|----------------------|-----|---------|-----------|
| Ilango 2015   | Australia | 3-4 | 167 vs 151                | Not reported                            | 81.3 years (10.5)     | 82.1 years (9.0)     |     | Incidence of postoperative delirium | Other postoperative complications | Post-discharge mortality |
| Juliebo 2009  | Norway    | 1 or 2 | 20 vs 337               | Patients aged 65 years and over         | 89/229                |                      |     | Delirium |           |           |
### Delirium: 85 years (82-89)
No delirium: 82 years (77-87)

M/F: 88/276

### Koval 1999
USA

| ASA 1 or 2: | ASA 3 or 4: |
|-------------|-------------|
| 236         | 120         |

| Spinal:     | General (n=362) v Spinal (n=280) |
|-------------|-----------------------------------|
| AS 1 or 2:  | 131                                |
| AS 3 or 4:  | 137                                |

Patients who sustained a hip fracture

- Mean age
  - General: 78.5 years
  - Spinal: 81.0 years

M/F: 129/513

### Retrospective Studies

| Retrospective Studies | General v Spinal v Peripheral nerve block | Patients undergoing hip fracture surgery | Patients aged 65 years and older | -Postoperative delirium |
|-----------------------|------------------------------------------|----------------------------------------|----------------------------------|--------------------------|
| Bellelli 2013         | Not reported | 392 included | Mean age: 83 years (SD 6) | Inpatient medical complication rate |
| ITALY Abstract        |-General v Spinal v Peripheral nerve block | Patients undergoing hip fracture surgery | Patients aged 65 years and older | Hospital mortality rate |

- 1 year mortality rate
| Study          | Country  | ASA 1: | ASA 2: | ASA 3: | Type of Surgery                           | Patients Aged | Complications                        |
|---------------|----------|--------|--------|--------|------------------------------------------|---------------|--------------------------------------|
| Kim 2013      | KOREA    | 6      | 311    | 189    | General (n=246) v Spinal (n=249) v Epidural (n=11) | 60-69 years n=83,  70-79 years n=227, >80 years n=196 | -30 day postoperative complications, Cardiac complications, Pulmonary complications, Delirium, Death |
| Konttinen 2006 | FINLAND  | 8      | 6      |        | General (n=3) v Spinal (n=11, single shot: 5, continuous: 6) | Patients aged 100 years and over | Intraoperative variables, Complications, Post-op discharge location, Pain management, Haemodynamics, Mental status, Mobilisation |
| Study | Country | Age | Setting | Patients | Control Measures | Outcome Measures |
|-------|---------|-----|---------|----------|------------------|------------------|
| Luger 2014 | Austria | 80+ | Patients scheduled for acute hip fracture surgery | Patients aged 80 years of age and older | Age | Cognitive decline, Time to surgery, Length of hospital stay, Pre and post nursing home stay, Comorbidities, Perioperative Complications |
| | | | General (n=116) v Regional (n=213) | No delirium: 88.8 years (SD 5.3, range 81-100) | M/F: 19/51 | |
| | | | Group 1 (post-op delirium): 2.9 +/- 0.6 | Age | |
| | | | Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 | Delirium: 87.9 years (SD 4.5, range 81-97) | |
| | | | Control: 2.8 +/- 0.6 | No delirium: 88.8 years (SD 5.3, range 81-100) | |
| Michael 2014 | UK Abstract | 60-100 | Hip fracture patients | Patients aged 60-100 years | Age | Pre and post-operative cognitive function |
| | | | General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia) | Age | |
| | | | 60-70 years n=50 | |
| | | | 70-80 years n=169 | |
| | | | 80-90 years 338 | |
| | | | 90-100 years | |
| O'Hara 2000 USA | General: ASA 1 or 2: 1698, ASA 3: 3666, ASA 4 or 5: 618 | General (n=6206) vs Regional (n=3219; spinal n=3078 and epidural n=141) | Hip fracture patients | Patients 60 years of age or older |
|----------------|-----------------------------------------------------|-------------------------------------------------|----------------------|----------------------------------|
|                | Age General: 60-69 years n=910, 70-79 years n=1918, 80-89 years n=2602, 90+ years n=776 | Age Regional: 60-69 years n=325, 70-79 years n=881, 80-89 years n=1452, 90+ years n=561 | M/F: 178/526 | M/F: 2010/7415 |

Primary:
- 30 day mortality
Secondary:
- 7 day mortality
Other:
- 7 day morbidity
| Shih | General (n=167) v Spinal (n=168) | Patients undergoing hip fracture repair | Patients aged 80 and over | Postoperative morbidity | Postoperative mortality | Pre and intraoperative variables |
|------|---------------------------------|----------------------------------------|---------------------------|------------------------|------------------------|-----------------------------|
| 2010 | ASA 2: 47                        | General: Mean age                      | General: 83.96 years (SD 3.71) |                        |                        |                             |
| TAIWAN | ASA 3: 115                       | Spinal: Mean age                       | Spinal: 84.93 years (SD 4.04) |                        |                        |                             |
|      | ASA 4: 1                         |                                        |                           |                        |                        |                             |
|      | Spinal:                           |                                        |                           |                        |                        |                             |
|      | ASA 2: 45                        |                                        |                           |                        |                        |                             |
|      | ASA 3: 120                       |                                        |                           |                        |                        |                             |
|      | ASA 4: 2                         |                                        |                           |                        |                        |                             |
### Table 2a: Quality assessment of RCT studies reporting delirium

| Study                        | Randomisation | Concealment of allocation | Similarity at baseline | Blinding of outcome assessor | Incomplete outcome data (for outcome of delirium) | Validity of assessment tool | Assessment tool specific for delirium | Selective reporting |
|------------------------------|---------------|----------------------------|-------------------------|------------------------------|--------------------------------------------------|-----------------------------|--------------------------------------|---------------------|
| **Parker & Griffiths 2015** | UNCLEAR       | LOW                        | Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group). | HIGH                         | LOW                                              | Unclear-no details            | Unclear                                      | UNCLEAR             |
| **Casati 2003**              | UNCLEAR       | LOW                        | Groups similar for all baseline characteristics measured. | UNCLEAR                       | LOW                                              | MMSE good validity for cognitive function | No                                    | UNCLEAR             |
| **Bigler 1985**              | UNCLEAR       | UNCLEAR                    | Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group. | LOW                           | UNCLEAR                                          | No                           | Insufficient information to permit judgement. |                      |

**NB** Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.
# Table 2b: Quality assessment of observational studies reporting delirium

| Study         | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|---------------|----------------------|----------------------|-------------------------------|--------------------------------|---------------------------|--------------------------------|
| Belleli 2013  | LOW                  | HIGH for unadjusted data | UNCLEAR                      | LOW                           | Yes                       | UNCLEAR                        |
| (Abstract)    |                      | LOW for adjusted data |                               |                               |                           | Patients with incomplete data in medical records were excluded from this study. Proportion not stated. |
| RETROSPECTIVE| Patients aged > 65 years admitted to one orthogeriatric unit between 2007 and 2011. | Baseline characteristics not presented for anaesthesia groups, but multivariate analysis for confounders. | No details | DSM-IV-TR criteria |                            |                                |
| Bitsch 2006   | UNCLEAR              | HIGH                 | UNCLEAR                       | LOW-good validity for cognitive function | No                        | HIGH                           |
| PROSPECTIVE   | Consecutive patients but large number excluded and unclear if similar characteristics to included | No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses. | No details | MMSE |                            | 12/96 (12.5%) and 35/96 (36%) patients not available for testing on day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier. |
| Björkelund 2010 | LOW                  | HIGH                 | UNCLEAR                       | LOW                           | No for Organic Brain Syndrome Scale and DSM-IV criteria | LOW                           |
| PROSPECTIVE   | Consecutive patients included | No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses. | No details | Organic Brain Syndrome Scale | No for DSM-IV criteria | Appears to be no loss to follow-up from included patients for delirium assessment |
| Gilbert 2000  | LOW                  | HIGH                 | UNCLEAR                       | LOW (MMSE) HIGH ("mental confusion") | Unclear | UNCLEAR                        |
| PROSPECTIVE   | Patients given general and spinal were drawn from the same population |Appear to be some baseline imbalances between general and regional groups, but multivariate analyses for all outcomes. | No details | Mental confusion not further defined; MMSE | No (MMSE) | No details-only how many included in final analysis |
| Ilango 2015   | LOW                  | HIGH                 | UNCLEAR                       | HIGH                          | Unclear | UNCLEAR                        |
| Study       | Eligibility criteria                                                                 | Confounders Low risk                                                                 | Blinding of outcome assessors | Validity of Assessment tool used                  | Tool specific for delirium | Loss to follow up/missing data |
|------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------|---------------------------|-------------------------------|
| PROSPECTIVE | All hip fracture patients admitted over a year                                         | Similar baseline characteristics (age, gender, pre-op cognitive function), but no adjusted analyses. | No details                  | Subjective method ("clinical judgement") and several scales; cut-off unclear. | Yes                       | 19/337 (6%) incomplete data. No details on characteristics. |
| **Juliebo 2009**  | **LOW**                                                                                   | **HIGH**                                                                               | **LOW**                      | CAM                                              |                           | **HIGH**                      |
| PROSPECTIVE | All eligible hip fracture patients September 2005 to December 2006.                    | Univariate analysis only for type of anaesthetic and outcome. No details on similarity of groups for this variable. Adjusted analyses not with type of anaesthetic as a variable. | Staff performing assessments were not involved in the care of enrolled patients | Yes | No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part. Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively and excluded. No details on their characteristics. |
| **Kim 2013**    | **LOW**                                                                                   | **HIGH**                                                                               | **UNCLEAR**                  | DSM-IV criteria                                  | Yes                       | **LOW**                       |
| RETROSPECTIVE | Consecutive sample of hip fracture patients                                              | No adjusted analyses including type of anaesthesia. No details on similarity of baseline characteristics for groups. | No details                  | Low                                              |                           | Appears to be no missing data |
| **Kontinnen 2006** | **LOW**                                                                                   | **HIGH**                                                                               | **UNCLEAR**                  | UNCLEAR Not clearly defined                      | Unclear                   | UNCLEAR                      |
| RETROSPECTIVE | All patients over 100 years old undergoing emergency Surgery in one hospital          | No adjusted analyses                                                                  | No details                  | DSM-IV criteria                                  |                           | No details on missing data/exclusions. |
| **Koval 1999** | **LOW**                                                                                   | **HIGH**                                                                               | **UNCLEAR**                  | UNCLEAR Not clearly defined                      | Unclear                   | UNCLEAR                      |
| PROSPECTIVE | Patients with hip fracture admitted to one hospital between 1987 and 95. Patient excluded if certain characteristics meant type of anaesthetic was pre-determined. | Some imbalances in baseline characteristics. Adjustment for covariates described but results presented appear to be unadjusted. | No details                  | UNCLEAR Not clearly defined                      | Unclear                   | 4.4% of patients lost to follow-up. No further details |

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| Study          | Eligibility criteria | Confounders         | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|---------------|----------------------|---------------------|-----------------------------|---------------------------------|---------------------------|-----------------------------|
| Luger 2014    | LOW                  | HIGH                | UNCLEAR                      | LOW (DSM-IV)                    | Yes (DSM-IV)              | HIGH                        |
| RETROSPECTIVE | Patients scheduled for acute hip fracture surgery at Innsbruck Medical University between 2005 and 2007 | No details on baseline characteristics between groups. No adjusted analyses. | No details | "Unspecified cognitive dysfunction behaviour" and DSM-IV | Unclear (unspecified) | 82/411 (20%) excluded due to incomplete records. Unclear if excluded had different characteristics to those included |
| Michael 2014  | LOW                  | HIGH                | UNCLEAR                      | LOW                             | Yes                       | UNCLEAR                     |
| (Abstract)    | RETROSPECTIVE        | Consecutive patients | No details on baseline characteristics between groups. No adjusted analyses. | No details | AMT | 34/738 (5%) excluded retrospectively. No reasons for exclusions. |
| O'Hara 2000   | LOW                  | HIGH for unadjusted data | LOW for adjusted data         | UNCLEAR                        | UNCLEAR                   | UNCLEAR                     |
| RETROSPECTIVE | Consecutive patients from 20 hospitals | Appear to be some baseline imbalances between groups, but multivariate analyses. | No details | Not clearly defined | 9425/9598 < 2% missing |
| Shih 2010     | LOW                  | HIGH                | UNCLEAR                      | UNCLEAR                        | Unclear                   | LOW                         |
| RETROSPECTIVE | Octogenarian patients undergoing hip fracture repair in one centre between 2002 and 2006. | Some baseline imbalances between groups; no adjusted analyses for delirium (only for "morbidity") generally. | No details | Not clearly defined | Appears to be no missing data from those patients included. |

NB Quality assessment was not performed for Atay [31] as a full translation was not available.
Table 3: Summary findings table of studies reporting adverse events. *OR = Odds Ratio
GA vs. RA; NR = not reported; NS = not significant

| POMS categories | Study            | Adverse event description | GA       | RA       | Summary statistic*/p-value |
|-----------------|------------------|---------------------------|----------|----------|----------------------------|
| Pulmonary       | Basques 2015     | Ventilatory support       | 58/7253 (0.8%) | 13/2589 (0.5%) | NR                         |
|                 |                  | Pneumonia                 | 261/7253 (3.6%) | 108/2589 (4.2%) | NR                         |
|                 | Bigler 1985      | Pneumonia                 | 2/20     | 1/20     | NR                         |
|                 | Chu 2015         | Respiratory Failure       | 868/5204 (1.61%) | 328/5204 (0.63%) | OR 2.71 (95%CI 2.38 to 3.01), p<0.001, Favours RA |
|                 |                  | Ventilatory support       | 4008/5204 (7.70%) | 338/5204 (1.44%) | OR 6.08 (95%CI 5.59 to 6.61), p<0.001, Favours RA |
|                 | Konttinen 2006    | Pneumonia                 | 0/3      | 2/11     | NR                         |
|                 | Le Liu 2014      | Overall pulmonary         | 18/172 (25%) | 27/145 (25.5%) | P=0.934 NS                  |
|                 |                  | Hypoxia                   | 19/72 (26.4%) | 23/145 (15.9%) | P=0.065 NS                  |
|                 | Le Wendling 2012 | Overall pulmonary         | 17/235 (6%) | 1/73 (1%) | OR 2.2 (95%CI 0.7 to 7.2) P=0.0841, Favours RA |
|                 | Naja 2000        | Hypoxia                   | 2/30 (6%) | 0/30 (0%) | NR                         |
|                 | Neuman 2012      | Overall pulmonary         | 1030/12904 (8.1%) | 359/5254 (6.8%) | P=0.005, Favours RA          |
|                 |                  | Respiratory Failure       | 1040/12904 (5%) | 178/5254 (3.4%) | P<0.0001, Favours RA        |
| Study                     | Disease                  | Event 1 | Event 2 | Odds Ratio (95% CI) | P-value | Conclusion |
|-------------------------|--------------------------|---------|---------|---------------------|---------|------------|
| O’Hara 2000             | Pneumonia                | 174/6206 (2.8%) | 84/3219 (2.6%) | OR 1.21 (0.87 to 1.68) | NS      |            |
| Shih 2010               | Overall pulmonary        | 11/167  (6.6%)  | 3/168   (1.8%)   | P<0.03              | Favours RA |            |
| Cardiovascular Basques 2015 | Myocardial infarction    | 137/7253 (1.9%) | 49/2859 (1.9%)   | NR                  |         |            |
| Cardiovascular Basques 2015 | Thromboembolic          | 138/7253 (1.9%) | 25/2589 (1.0%)   | NR                  |         |            |
| Bigler 1985             | Cardiovascular decompensation | 1/20  | 1/20   | NR                  |         |            |
| Bigler 1985             | Pulmonary embolism       | 1/20  | 1/20   | NR                  |         |            |
| Chu 2015                | Myocardial infarction    | 188/5204 (3.6%) | 169/5204 (3.2%) | OR 1.11 (0.9 to 1.37), p=0.31 | NS      |            |
| Fields 2015             | Thromboembolism          | 1.64% | 0.72%  | P=0.004             | Favours RA |            |
| Konttinen 2006          | Myocardial infarction    | 0/3   | 1/11   | NR                  |         |            |
| Le Wendling 2012        | All cardiovascular complications | NR  | NR    | OR 1.7 (95% CI 0.4 to 6.3) | NS      |            |
| Seitz 2014              | Deep vein thrombosis     | 47/8818 (0.5%) | 41/12155 (0.3%) | P=0.03             | NS when matched |            |
| Seitz 2014              | Pulmonary Embolism       | 100/8818 (1.1%) | 93/12155 (0.8%) | P=0.006             | NS when matched |            |
| Sutcliffe 1994          | Deep vein thrombosis     | 16/950 (1.7%) | 14/383 (3.7%)   | P<0.05              | NS       |            |
| Sutcliffe 1994          | Pulmonary Embolism       | NR    | NR    | NS                  |         |            |
| Infectious              | Bigler 1985              | Wound infection | 1/20  | 0/20   | NR                  |         |            |
| Fields 2015             | Urinary Tract infection  | 5.76% | 8.87%  | P<0.0001            | Favours GA |            |
| Study              | Outcome                      | Cases   | Controls  | p-value   |
|--------------------|------------------------------|---------|-----------|-----------|
| Rashid 2013        | Urinary Tract Infection      | NR      | NR        | NS        |
| Basques 2015       | Wound Infection              | 94/7253 (1.3%) | 39/2589 (1.5%) | NS        |
| Renal              |                              | NR      | NR        | OR 0.92 (95%CI 0.61 to 1.4) NS  |
| Basques 2015       | Acute Renal Failure          | 29/7253 (0.4%) | 10/2589 (0.4%) | NS        |
| Bigler 1985        | Urinary retention            | 4/20    | 5/20      | NS        |
| Chu 2015           | Acute Renal Failure          | 78/52043 (0.15%) | 56/52044 (0.11%) | P=0.06 NS  |
| Naja 2000          | Acute Renal Failure          | 2/30 (6%) | 0/30 (0%) | NS        |
| Overall complications | Serious medical complications | 55/311 (17.7%) | 79/430 (18.4%) | OR 1.29 (95%CI 1.13 to 1.47), p=0.0002, Favours RA |
| Gilbert 2000       | Less medical complications   | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95%CI 0.90 to 1.82) NS  |
| Whiting 2015       | Surgical complications       | 15/311 (4.8%) | 19/430 (4.4%) | OR 1.08 (95%CI 0.65 to 1.21) NS  |
| Major complications | NR                           | NR      | OR 1.43 (95%CI 1.16-1.77) NS  |
| Whiting 2015       | Minor complications          | NR      | NR        | OR 1.02 (95%CI 0.82 to 1.26) NS  |
| Fields 2015        | All complications            | NR      | NR        | OR 1.24 (95%CI 1.05 to 1.48) NS  |
| All complications  |                              | 2357/4813 (48.97%) | 830/1815 (45.75%) | OR 1.29 (95%CI 1.13 to 1.47), p=0.0002, Favours RA |
| Hekimoglu Sahin 2012 | All complications           | NR      | NR        | NS        |
| Ilango 2015        | All complications            | NR      | NR        | NS        |
| Koval 1999         | All complications            | 41/362 (11.3%) | 32/280 (11.4%) | NS        |
| Le Liu 2014        | All complications            | 17/72 (23.6%) | 50/145 (34.5%) | P=0.165 NS  |
| Study            | Type                      | Measure                  | Le Wendling 2012 | Radcliffe 2013 | Shih 2010 | Chu 2015 (ITU admissions) | Chu 2015 (ITU stay >3 days) | Baumgarten 2012 | Casati 2003 | Maia 2014 | Minville 2008 | Messina 2013 | Basques 2015 | Fields 2015 |
|------------------|---------------------------|--------------------------|------------------|---------------|-----------|---------------------------|--------------------------|----------------|------------|------------|--------------|--------------|--------------|-------------|
|                  | All complications         | NR                       | NR               | 22%           | 19%       | 21/167 (12.6%)            | 9/168 (5.4%)            |               |            |            |              |              |              |
|                  | All complications         | NR                       | NR               | 19%           | Log regression model p=0.002 | Favours RA              |                           |               |            |            |              |              |              |
|                  | All complications         | 22%                      | 19%              | P<0.02        |           | 5743/520 (11.03%)         | 3205/520 (6.16%)         | OR 1.95 (95%CI 1.87 to 2.05), p<0.001 | Favours RA |
|                  | Specific complications    |                          |                  |               |           | 1206/520 (2.32%)          | 411/5204 (0.79%)         |                           | P<0.001     |
|                  | ITU stay >3 days          |                          |                  |               |           | 10/328 (3.0%)             | 18/313 (5.8%)            | OR 1.3 (95%CI 1.0-1.6) | Favours GA |
|                  | Pressure ulcers           |                          |                  |               |           | 12/15 (80%)               | 7/15 (46%)               |                           | P=0.05      |
|                  | Hypotension requiring crystalloid infusion |              |                  |               |           |                           |                          |                           |            |
|                  |                           |                          |                  |               |           |                           |                          |                           |            |
|                  | Intraoperative hypotension|                          |                  |               |           | 25/50 (83%)               | 80/173 (68%)             |                           | P=0.014     |
|                  |                           |                          |                  |               |           |                           |                          |                           |            |
|                  | Haemodynamic changes first 10min |              |                  |               |           |                           |                          |                           |            |
|                  | Blood transfusion         | 2843/725 (39.2%)         | 851/2589 (32.9%) | Matched OR 1.34 (1.22 to 1.49), p<0.001 | Favours RA              |                           |                           |            |
|                  | Blood transfusion         | 45.49%                   | 39.34%           | P<0.0001     |           |                           |                          |                           |            |

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| Study             | Outcome   | Event 1 | Event 2 | p-value    |
|-------------------|-----------|---------|---------|------------|
| Minville 2008     | Blood transfusion | 23%     | 4%      | P<0.05     |
| Shih 2010         | Blood loss | Median 250 (0-1600) ml | Median 200 (0-1200) ml | P=0.01     |
| Chu 2015          | Stroke    | 840/5204 (1.61%) | 717/5204 (1.38%) | OR 1.18 (95%CI 1.07 to 1.31), p=0.001 |
| Le Liu 2014       | Stroke    | 5/72 (5.9%) | 4/145 (2.8%) | P=0.145 NS |
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Studies included in systematic review n=89

Citations excluded after screening of titles/abstracts n=2524

Articles retrieved for detailed evaluation n=323

Citations excluded after screening of titles/abstracts n=2524

Excluded duplicate citations n=1376

Total citations left to screen n=2847

Articles excluded n=234
- Study design n=90
- Could not locate n=11
- Duplicates n=28
- Incorrect population n=6
- No anaesthesia data n=33
- Outdated anaesthesia n=30
- Results not reported in relation to type of anaesthesia n=12
- Inappropriate comparison n=18
- Inappropriate outcome n=6

Citations identified by electronic searches n=4222

Citations identified through other sources n=1

Identification

Screening

Eligibility

Included
Figure 1: Flowchart showing study selection process
Appendix 1: Example of search strategy

1 exp Hip fracture/  
2 hip fracture.mp.  
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.  
4 or/1-3  
5 exp an$esthesia/  
6 an$esthesia.mp.  
7 (anesthe$ or anaesthe$).tw.  
8 an$ethetic.mp.  
9 exp anesthetics/  
10 exp general an$esthesia/  
11 general an$esthesia.mp.  
12 Anesthesia/ (43366)  
13 exp Anesthesia, General/  
14 general an$esthesia.mp.  
15 sedation.mp. (28516)  
16 exp regional an$esthesia/  
17 regional an$esthesia.mp.  
18 peripheral an$esthesia.mp.  
19 central blockade.mp.  
20 central block.mp.  
21 exp spinal an$esthesia/  
22 spinal an$esthesia.mp.  
23 exp epidural an$esthesia/  
24 epidural an$esthesia.mp.  
25 exp local an$esthesia/  
26 local an$esthesia.mp.  
27 infiltrative an$esthesia.mp.  
28 peripheral nerve block.mp.  
29 intravenous regional an$esthesia.mp.  
30 systemic local an$esthesia.mp.  
31 exp nerve block$/  
32 nerve block$.mp.  
33 neuroaxial blockade.mp.  
34 Anesthesia/ or exp Anesthesia, Intravenous/  
35 exp inhalation an$esthesia/  
36 inhalation an$esthesia.mp.  
37 or/5-36  
38 4 and 37
### Appendix 2: Table of eligible on-going studies

| Title                                                                 | ID             | Comparison          | Status                                         | Design                          | Contact                                      | Country     |
|----------------------------------------------------------------------|----------------|---------------------|------------------------------------------------|---------------------------------|----------------------------------------------|-------------|
| Variations in Anaesthesia care for hip fracture surgery               | NCT02787031    | General v Neuraxial | Recruitment completed but no results available | Retrospective observational cohort | Ottawa Hospital Research Institute           | Canada      |
| A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia | NCT02190903    | General v Spinal    | Recruitment completed but no results available | Open label randomised trial      | Mark D Neuman                                | USA         |
| Regional versus general anaesthesia for promoting independence after hip fracture | NCT02507505    | General v Regional  | Recruiting patients                             | Double blind randomised trial   | Mark Powell/ Mark Neuman                     | USA         |
| Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery | NCT02213380    | General v Regional  | Recruiting patients                             | Open label randomised controlled trial | Ting Li/ Sishi Chen                          | China       |
| Study Title                                                                 | NCT Number               | Anaesthesia Type              | Recruitment Status                        | Study Design                       | Investigator(s)          | Country       |
|----------------------------------------------------------------------------|--------------------------|-------------------------------|-------------------------------------------|------------------------------------|--------------------------|---------------|
| The safety of anaesthesia management for traumatic hip surgery in elderly  | NCT02692989              | General v Regional             | Ongoing, but not recruiting patients      | Retrospective observational cohort  | Subhi M Alghanem        | Jordan        |
| Anaesthesia and post-operative mortality after proximal femur fractures    | NCT02406300              | Peripheral nerve block/General v Subarachnoid anaesthesia | Enrolling patients by invite only         | Double blind randomised controlled trial | Raul Carvalho           | Portugal      |
| Effect of anaesthesia in fracture healing                                  | NCT02621255              | General v Regional             | Recruiting patients                       | Double blind randomised trial       | Ebru Biricik            | Turkey        |
| Mortality following surgery for proximal femoral fractures                 | NCT01807039              | General vs. Subarachnoid anaesthesia | Study has been completed                  | Retrospective observational cohort  | Petr Štourač            | Czech Republic|
| Practice survey on femoral neck fractures and the incidence of type of anaesthesia on patient outcome | NCT02198820              | General v Regional             | **WITHDRAWN                               | Prospective observational cohort     | Eric P Deflandre       | Belgium       |

**ICRP**

| Study Title                                                                 | IRCT Number              | Anaesthesia Type              | Status                        | Study Design                       | Investigator(s)          | Country       |
|----------------------------------------------------------------------------|--------------------------|-------------------------------|-------------------------------|------------------------------------|--------------------------|---------------|
| Hemodynamic effects of general                                              | IRCT201308316280N4       | General v                     | Completed                     | Double blind                       | Mohammad                | Iran          |
| and spinal anaesthesia for hip fracture surgery | Spinal | randomised trial | Haghighi |
|-----------------------------------------------|--------|-----------------|-----------|

**Appendix 3**

**Figure 3:** Forest plot of unadjusted and adjusted studies reporting mortality. RR = relative risk; RA = regional anaesthesia; CI = confidence interval.

![Forest plot of unadjusted and adjusted studies reporting mortality](image)
Appendix 4

Figure 4: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval
### Appendix 5

**Table 3: Summary findings table of studies reporting adverse events.** *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant*

| POMS categories | Study         | Adverse event description | GA                | RA                | Summary statistic*/p-value |
|-----------------|---------------|----------------------------|-------------------|-------------------|---------------------------|
| Pulmonary       | Basques 2015  | **Ventilatory support**    | 58/7253 (0.8%)    | 13/2589 (0.5%)    | NR                        |
|                 |               | **Pneumonia**               | 261/7253 (3.6%)   | 108/2589 (4.2%)   | NR                        |
|                 | Bigler 1985   | **Pneumonia**               | 2/20              | 1/20              | NR                        |
|                 | Chu 2015      | **Respiratory Failure**     | 868/52043 (1.61%) | 328/52044 (0.63%) | OR 2.71 (95%CI 2.38 to 3.01), p<0.001 Favours RA |
|                 |               | **Ventilatory support**     | 4008/52043 (7.70%)| 338/52044 (1.44%) | OR 6.08 (95%CI 5.59 to 6.61), p<0.001 Favours RA |
|                 | Konttinen 2006| **Pneumonia**               | 0/3               | 2/11              | NR                        |
|                 | Le Liu 2014   | **Overall pulmonary**       | 18/172 (25%)      | 27/145 (25.5%)    | P=0.934 NS                |
|                 |               | **Hypoxia**                 | 19/72 (26.4%)     | 23/145 (15.9%)    | P=0.065 NS                |
|                 | Le Wendling 2012| **Overall pulmonary**   | 17/235 (6%)      | 1/73 (1%)         | OR 2.2 (95%CI 0.7 to 7.2) P=0.0841 Favours RA |
|                 | Naja 2000     | **Hypoxia**                 | 2/30 (6%)         | 0/30 (0%)         | NR                        |
|                 | Neuman 2012   | **Overall pulmonary**       | 1030/12904 (8.1%)| 359/5254 (6.8%)   | P=0.005 Favours RA        |
|                 |               | **Respiratory Failure**     | 1040/129         | 178/5254          | P<0.0001                  |
| Study            | Category               | Event                                 | Cases | Controls | OR (95% CI)      | P Value | Conclusion       |
|------------------|------------------------|---------------------------------------|-------|----------|------------------|---------|------------------|
| O'Hara 2000      | Pneumonia              | 174/6206 (2.8%)                       | 84/3219 (2.6%) | OR 1.21 (0.87 to 1.68) NS |
| Shih 2010        | Overall pulmonary      | 11/167 (6.6%)                         | 3/168 (1.8%) | P<0.03 Favours RA |
| Cardiovascular   | Basques 2015           | Myocardial infarction                 | 137/7253 (1.9%) | 49/2859 (1.9%) | NR |
|                  | Thromboembolic         | 138/7253 (1.9%)                       | 25/2589 (1.0%) | NR |
| Bigler 1985      | Cardiovascular         | 1/20                                  | 1/20 | NR |
|                  | Pulmonary embolism     | 1/20                                  | 1/20 | NR |
| Chu 2015         | Myocardial infarction  | 188/5204 (3.06%)                      | 169/5204 (4.032%) | OR 1.11 (95%CI 0.9 to 1.37), p=0.31 NS |
| Fields 2015      | Thromboembolism        | 1.64%                                 | 0.72% | P=0.004 Favours RA |
| Konttinen 2006   | Myocardial infarction  | 0/3                                   | 1/11 | NR |
| Le Wendling 2012 | All cardiovascular complications | NR | NR | OR 1.7 (95%CI 0.4 to 6.3) NS |
| Seitz 2014       | Deep vein thrombosis   | 47/8818 (0.5%)                        | 41/12155 (0.3%) | P=0.03 NS when matched |
|                  | Pulmonary Embolism     | 100/8818 (1.1%)                       | 93/12155 (0.8%) | P=0.006 NS when matched |
| Sutcliffe 1994   | Deep vein thrombosis   | 16/950 (1.7%)                         | 14/383 (3.7%) | P<0.05 NS |
|                  | Pulmonary Embolism     | NR                                    | NR | NS |
| Infectious       | Bigler 1985            | Wound infection                       | 1/20 | 0/20 | NR |
| Fields 2015      | Urinary Tract          | 5.76%                                 | 8.87% | P<0.0001 |
| Study                      | Event                  | Number | Rate (%) | OR (95% CI)          |
|----------------------------|------------------------|--------|----------|----------------------|
| Rashid 2013                | Urinary Tract infection| NR     | NR       | NS                   |
| Basques 2015               | Wound infection        | 94/7253 (1.3%) | 39/2589 (1.5%) | NS                   |
| Renal                      | Basques 2015           | 29/7253 (0.4%) | 10/2589 (0.4%) | NS                   |
| Bigler 1985                | Urinary retention      | 4/20   | 5/20     | NS                   |
| Chu 2015                   | Acute Renal Failure    | 78/52043 (0.15%) | 56/52044 (0.11%) | P=0.06 NS           |
| Naja 2000                  | Acute Renal Failure    | 2/30 (6%) | 0/30 (0%)  | NS                   |
| Overall complications      | Gilbert 2000           | 55/311 (17.7%) | 79/430 (18.4%) | OR 0.92 (95% CI 0.61 to 1.4) NS |
|                           | Gilbert 2000           | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95% CI 0.90 to 1.82) NS |
|                           | Whiting 2015           | 15/311 (4.8%) | 19/430 (4.4%) | OR 1.08 (95% CI 0.65 to 1.21) NS |
|                           | Surgical complications | NR     | NR       | OR 1.43 (95% CI 1.16-1.77) NS |
|                           | Major complications    | NR     | NR       | OR 1.43 (95% CI 1.16-1.77) NS |
|                           | Gilbert 2000           | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95% CI 0.90 to 1.82) NS |
|                           | Whiting 2015           | 15/311 (4.8%) | 19/430 (4.4%) | OR 1.08 (95% CI 0.65 to 1.21) NS |
|                           | Fields 2015            | NR     | NR       | OR 1.02 (95% CI 0.82 to 1.26) NS |
|                           | All complications      | NR     | NR       | OR 1.24 (95% CI 1.05 to 1.48) NS |
|                           | All complications      | 2357/4813 (48.97%) | 830/1815 (45.75%) | OR 1.29 (95% CI 1.13 to 1.47), p=0.0002, Favours RA |
|                           | All complications      | NR     | NR       | NS                   |
| Hekimoglu Sahin 2012       | All complications      | NR     | NR       | NS                   |
| Ilango 2015                | All complications      | NR     | NR       | NS                   |
| Koval 1999                 | All complications      | 41/362 (11.3%) | 32/280 (11.4%) | NS                   |
| Le Liu 2014                | All complications      | 17/72  | 50/145   | P=0.165 NS           |
| Study               | Event Type          | All Complications | Specific Complications |
|---------------------|---------------------|-------------------|------------------------|
| Le Wendling 2012    | All complications   | NR                | (23.6%) (34.5%)        |
| Radcliffe 2013      | All complications   | 22%               | 19%                    |
| Shih 2010           | All complications   | 21/167 (12.6%)    | 9/168 (5.4%)           |
| Chu 2015            | ITU admissions      | 5743/520 (11.03%) | 3205/520 (6.16%)       |
| Baumgarten 2012     | Pressure ulcers     | 10/328 (3.0%)     | 18/313 (5.8%)          |
| Casati 2003         | Hypotension         | 12/15 (80%)       | 7/15 (46%)             |
| Maia 2014           | Intraoperative      | 25/50 (50%)       | 80/173 (46%)           |
| Minville 2008       | Intraoperative      | 35/42 (83%)       | 74/109 (68%)           |
| Messina 2013        | Haemodynamic changes first 10min | Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA |
| Basques 2015        | Blood transfusion   | 2843/725 (39.2%) | 851/2589 (32.9%)       |
| Study            | Comparison       | Event                    | Events | Events | P-value | Conclusion |
|------------------|------------------|--------------------------|--------|--------|---------|------------|
| Fields 2015      | Blood transfusion| 45.49%                  | 39.34% | P<0.0001 | Favours RA |
| Minville 2008    | Blood transfusion| 23%                     | 4%     | P<0.05  | Favours RA |
| Shih 2010        | Blood loss       | Median 250 (0-1600) ml    | Median 200 (0-1200) ml | P=0.01 | Favours RA |
| Chu 2015         | Stroke           | 840/5204 3 (1.61%)       | 717/5204 4 (1.38%) | OR 1.18 (95%CI 1.07 to 1.31), p=0.001 | Favours RA |
| Le Liu 2014      | Stroke           | 5/72 (5.9%)              | 4/145 (2.8%) | P=0.145 NS |
Appendix 6

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| Study            | Assessment tool          | Time-point         | RR (95% CI)     |
|------------------|--------------------------|--------------------|-----------------|
| BCT              | Unspecified              | Unspecified        | 0.11 (0.01, 1.14) |
| Casali 2003      | MMSE 24 point decline    | Day 1 post-op     | 1.13 (0.60, 2.21) |
| Casali 2003      | MMSE 24 point decline    | Day 7 post-op     | 3.00 (0.35, 25.68) |
| Karmakar 2003    | CAM                      | Day 0-1           | 0.68 (0.26, 1.60) |
| Karmakar 2003    | CAM                      | Day 1-2           | 1.13 (0.35, 3.46) |
| Karmakar 2003    | CAM                      | Day 2-3           | 1.81 (0.18, 18.99) |
| Karmakar 2003    | CAM                      | Day 3-4           | 2.73 (0.12, 69.19) |
| ESRD              |                          |                   |                 |
| Björkland 2010   | OBS + DSM-IV             | After 8 hours minimum post-op | 1.23 (0.58, 2.52) |
| Björkland 2010   | OBS + DSM-IV             | After 8 hours minimum post-op | 0.98 (0.22, 3.90) |
| Arango 2015      | Clinical judgement + etha obs chart | Any time during postoperative recovery | 0.98 (0.70, 1.40) |
| Jiteng 2009      | CAM                      | Up to 5 days post-op | 0.49 (0.14, 1.73) |
| Koval 1999       | Unspecified              | Not specified     | 0.38 (0.12, 1.28) |
| Retrospective    |                          |                   |                 |
| Kim 2013         | DSM-IV                   | Within 30 days    | 1.17 (0.72, 1.89) |
| Kuroda 2009      | Unspecified              | Within 6 days post-op | 0.88 (0.19, 3.90) |
| Luger 2014       | DSM-IV                   | Not specified     | 1.47 (0.60, 3.52) |
| Luger 2014       | DSM-IV or UCDS           | Not specified     | 1.30 (0.86, 1.87) |
| Ohara 2000       | Unspecified              | Within 7 days     | 0.73 (0.48, 1.10) |
| Shen 2010        | Unspecified              | Before discharge  | 0.04 (0.73, 49.50) |

RR>1 favours regional anaesthesia
Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.
Figure 3: Forest plot of unadjusted and adjusted studies reporting mortality. RR = relative risk; RA = regional anaesthesia; CI = confidence interval.
| Study          | Design     | Anaesthesia Type       | WMD (95% CI)   |
|---------------|------------|------------------------|----------------|
| **RCT**       |            |                        |                |
| Parker 2015   | RCT        | Spinal                 | 0.30 (-2.79, 3.39) |
| **Adjusted**  |            |                        |                |
| Chu 2015      | Retrospective | Neuraxial             | -0.33 (-0.42, -0.24) |
| Le-Wendling 2012 | Retrospective | Regional             | -0.19 (-0.27, -0.11) |
| Seitz 2014    | Retrospective | Regional             | -0.10 (-0.88, 0.68) |
| **Unadjusted**|            |                        |                |
| Naja 2000     | Prospective | Combined Sciatic/ PNB | -6.90 (-9.23, -4.57) |
| Hekimoglu Sahin 2012 | Retrospective | Spinal & Epidural | 0.28 (-2.23, 2.79) |
| Le Liu 2014   | Retrospective | Peripheral nerve blocka | -0.57 (-1.84, 0.70) |
| Rashid 2013   | Retrospective | Regional             | -0.72 (-2.59, 1.15) |
| Sykora 1988   | Retrospective | Epidural             | -8.20 (-11.19, -5.21) |
Figure 4: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval
Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37
**Appendix B: Table of eligible on-going studies**

| Title                                                                 | ID            | Comparison       | Status                                           | Design                      | Contact                      | Country   |
|----------------------------------------------------------------------|---------------|------------------|--------------------------------------------------|-----------------------------|------------------------------|-----------|
| Variations in Anaesthesia care for hip fracture surgery               | NCT02787031  | General v Neuraxial | Recruitment completed but no results available | Retrospective observational cohort | Ottawa Hospital Research Institute | Canada    |
| A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia | NCT02190903  | General v Spinal | Recruitment completed but no results available | Open label randomised trial  | Mark D Neuman                 | USA       |
| Regional versus general anaesthesia for promoting independence after hip fracture | NCT02507505  | General v Regional | Recruiting patients                             | Double blind randomised trial | Mark Powell/ Mark Neuman     | USA       |
| Effect of anaesthesia on post-operative delirium in elderly patients undergoing | NCT02213380  | General v Regional | Recruiting patients                             | Open label randomised controlled trial | Ting Li/ Sishi Chen           | China     |
| Study Title                                                                 | NCT Identifier | Treatment | Status                        | Study Type                     | Authors                      | Country          |
|---------------------------------------------------------------------------|----------------|-----------|-------------------------------|--------------------------------|------------------------------|------------------|
| The safety of anaesthesia management for traumatic hip surgery in elderly | NCT02692989    | General v Regional | Ongoing, but not recruiting patients | Retrospective observational cohort | Subhi M Alghanem             | Jordan           |
| Anaesthesia and post-operative mortality after proximal femur fractures   | NCT02406300    | Peripheral nerve block/ General v Subarachnoid anaesthesia | Enrolling patients by invite only | Double blind randomised controlled trial | Raul Carvalho         | Portugal         |
| Effect of anaesthesia in fracture healing                                 | NCT02621255    | General v Regional | Recruiting patients            | Double blind randomised trial   | Ebru Biricik              | Turkey           |
| Mortality following surgery for proximal femoral fractures                | NCT01807039    | General vs. Subarachnoid anaesthesia | Study has been completed       | Retrospective observational cohort | Petr Štourač                 | Czech Republic   |
| Practice survey on femoral neck fractures and the incidence of type of anaesthesia on | NCT02198820    | General v Regional | **WITHDRAWN**                  | Prospective observational cohort | Eric P Deflandre           | Belgium          |
| Patient outcome | ICTRP | Complete | Study Design | Authors | Country |
|----------------|-------|----------|--------------|---------|---------|
| Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery | IRCT201308316280N4 General Spinal | Completed | Double blind randomised trial | Mohammad Haghighi | Iran |
| Section/topic     | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|------------------|---|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| TITLE            |   | Title 1 Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                       | 1                 |
| ABSTRACT         |   | Structured summary 2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2-3               |
| INTRODUCTION     |   | Rationale 3 Describe the rationale for the review in the context of what is already known.                                                                                                                      | 4-5               |
|                  |   | Objectives 4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                              | 5                 |
| METHODS          |   | Protocol and registration 5 Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                | 5                 |
|                  |   | Eligibility criteria 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6                 |
|                  |   | Information sources 7 Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.     | 5                 |
|                  |   | Search 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                        | 5                 |
|                  |   | Study selection 9 State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                | 6                 |
|                  |   | Data collection process 10 Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.            | 6                 |
|                  |   | Data items 11 List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                               | 6                 |
|                  |   | Risk of bias in individual studies 12 Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 8-12              |
|                  |   | Summary measures 13 State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                             | 15-25             |
|                  |   | Synthesis of results 14 Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                 | 8-12              |
## PRISMA 2009 Checklist

| Section/topic          | # | Checklist item                                                                 | Reported on page # |
|------------------------|---|---------------------------------------------------------------------------------|--------------------|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 26-29 |
| Additional analyses    | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 7 |

### RESULTS

| Study selection        | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8-12 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 15-25 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 12-15 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 1, 2, 3 |
| Synthesis of results   | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | Figure 1, 2, 3 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 26-29 |
| Additional analysis    | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA |

### DISCUSSION

| Summary of evidence    | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 12-13 |
| Limitations            | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). | 12-15 |
| Conclusions            | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 12-15 |

### FUNDING

| Funding                | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 15 |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.
The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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| <b>Primary Subject Heading</b>: | Anaesthesia |
| Secondary Subject Heading: | Geriatric medicine |
| Keywords: | General anaesthesia, Regional anaesthesia, Hip fracture, Delirium & cognitive disorders < PSYCHIATRY, Systematic review |
Title Page

The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Abstract

Background
Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium.

Objective
This systematic review will investigate the impact of anaesthetic technique on post-operative delirium. Other outcomes included mortality, length of stay, complications and functional outcomes.

Design
Systematic review of randomised controlled trials and non-randomised controlled studies.

Data Sources
Bibliographic databases were searched from inception to October 2016. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers were searched to identify ongoing trials.

Eligibility criteria
Studies were eligible if general and regional anaesthesia were compared in patients (aged 60 and over) undergoing hip fracture surgery, reporting primary outcome of post-operative delirium and secondary outcomes of mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life. Exclusion criteria were anaesthetic technique or drug not considered current standard practice; patients undergoing hip fracture surgery alongside other surgery and uncontrolled studies.

Results
Eighty-nine studies were included. There was no evidence to suggest that anaesthesia type influences post-operative delirium or mortality. Some studies suggested a small reduction in length of hospital stay with regional anaesthesia. There was some evidence to suggest that respiratory complications and intraoperative hypotension were more common with general anaesthesia. Heterogeneity precluded meta-analysis. All findings were described narratively and data were presented where possible in forest plots for illustrative purposes.

Conclusions

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodological rigorous study.

This review is registered with PROSPERO (CRD42015020166).


**Strengths and limitations of this study**

- This systematic review provides an update to evidence that examines whether the type of anaesthesia affects the development of post-operative delirium in patients with hip fractures.
- The review included randomised and non-randomised studies that included one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.
- Other outcomes were mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
**Introduction**

There are an estimated 70 000-75 000 hip fractures in the UK each year with an annual cost of £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current illness [3] and are at risk of mortality and significant morbidity. In 2014, the National Hip Fracture Database reported 30-day mortality as 7.5%. [4] Following surgery, adverse outcomes can include delirium, myocardial infarction, pneumonia, and cerebrovascular accident. [5]

Delirium is a common neuropsychiatric syndrome defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as the disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day. [6,7] Post-operative delirium has been reported to affect between 32%-53.3% of patients and is associated with prolonged hospital stay, discharge to care homes, difficulty in regaining function in activities of daily living and increased risk of development of cognitive dysfunction and dementia in the future. [8–13] The aetiology of delirium is multifactorial, with both modifiable and non-modifiable risk factors. [14,15] There is no known treatment for delirium, however a careful approach in the peri-operative period may reduce its incidence and severity. [6,9,15–18] Guideline committees have cautiously recommended that regional anaesthesia should be given unless contraindicated. [1,9,19] Despite this, the type of anaesthesia administered in patients with hip fractures remains varied. [4]

Ninety-eight percent of patients with hip fracture are offered surgery and will require anaesthesia. [5] Anaesthesia can be broadly classified into general (GA) or regional anaesthesia (RA). RA uses neuraxial blocks that avoid the use of GA drugs and opiates which have been linked to post-operative delirium. [3] Excessive depth of anaesthesia and perioperative hypotension have been reported in GA patients and are both
associated with an increased risk of mortality. [20] However, the risk of perioperative hypotension and sedation is not completely eradicated with RA. [21,22]

Findings from previous systematic reviews looking at the effects of type of anaesthesia on post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of out-dated anaesthetic drugs that are no longer relevant to current clinical practice. [5,24] Further limitations were the inclusion of only randomised controlled trials, [3,5,23,24] lack of focus on delirium as a primary outcome, [3,5,22,24,26] a limited search strategy [22] and restrictive selection criteria (e.g. exclusion of studies with patients with cognitive impairment). [23,25,26] Inadequate exploration of heterogeneity relating to delirium assessment and rating scales and assessment time points was also common. This systematic review aims to provide an up-to-date, comprehensive and methodologically robust analysis to examine the effect of RA versus GA on post-operative delirium and other outcomes in older patients undergoing surgery for hip fracture.

**Methods**

The protocol for this systematic review has been published and is registered with PROSPERO (CRD42015020166). [27] A summary of the methods is outlined below. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [28]

**Search strategy and selection criteria**

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to October 2016 using a combination of index terms and key words relating to the population, intervention and comparator (see Appendix A for sample search strategy). There was no restriction by search date, study design or language. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial
registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

**Study selection**

Studies were eligible for inclusion if they met the following pre-defined criteria:

1) Population - patients aged ≥60 years (or with a majority ≥60) undergoing surgery for fragility hip fracture.

2) Intervention and comparator – one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK [19]

3) Outcomes – primary outcome: post-operative delirium (any criteria as defined by study authors); secondary outcomes: mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.

4) Randomised or non-randomised controlled studies (prospective or retrospective).

Exclusion criteria for the primary outcome of ‘post-operative delirium’ were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthetic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and uncontrolled studies. Two reviewers (RC, VP) independently screened titles and abstracts. Any disagreements were resolved with the support of JY. Reasons for exclusion were recorded at the full text stage.

**Data Extraction and Quality Assessment**

A piloted, standardised data extraction form was used to record information on study design, patient characteristics, type of surgery, anaesthesia type, and outcomes. The Cochrane Collaboration risk of bias tool [29] was used to assess the methodological quality of randomised controlled trials and the Newcastle-Ottawa scale [30] for non-randomised studies. Full translations could not be obtained for three included studies.
[31–33], extracted data is therefore based mainly on numerical data and the English abstract. Data was extracted by RC and VP, with data checking by JY (for RC) and JD (for VP).

**Data analysis and synthesis**

Findings were grouped according to outcome. Where there was sufficient data, results were presented in forest plots (delirium, mortality and length of hospital stay). Effect estimates were not pooled as clinical and methodological heterogeneity was considered to be too great. Forest plots were thus used for illustrative purposes only and potential sources of heterogeneity (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. results reported narratively only, or a p-value only stated) results or conclusions from the study were nonetheless described in order to report the totality of the available evidence. Occurrence of delirium and mortality were reported as relative risks or odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative morbidity survey (POMS) criteria. [34] Findings for other outcomes (functional outcomes, quality of life, and discharge location) were reported narratively as heterogeneity and/or a paucity of data precluded representation in forest plots. Formal sensitivity analysis according to study quality, and assessment of publication bias using funnel plots were not possible.

**Patient and Public Involvement**

This systematic review is part of a programme of research looking at impact of anaesthesia on post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS Foundation Trust.

**Results**
Of 4223 citations screened, 89 studies met the eligibility criteria (Figure 1). There were 5 randomised controlled trials (RCTs), 28 prospective and 56 retrospective controlled studies.

Eighteen studies reported delirium (4 RCTs, [35–38] 7 prospective [18,39–44] and 7 retrospective studies [45–51]; 52 studies reported mortality (2 RCTs, [35,38] 10 prospective [41,44,52–59] and 40 retrospective studies [4,20,21,31,32,45,48,49,51,60–90]); 21 studies reported length of hospital stay (2 RCTs, [36,38] 5 prospective, [41,44,54,91,92] and 14 retrospective studies [21,48,53,62,64,65,69,72,74–77,89,93]); 25 studies reported adverse events (3 RCTs [35,36,94] 7 prospective [41,42,44,54,91,95,96] and 15 retrospective studies [20,21,45,48,49,62,63,65,69,73–75,89,90,97]); 8 studies reported functional outcome (2 RCTs, [35,36] 3 prospective [41,44,98] and 3 retrospective studies [58,67,99]) and 3 studies reported discharge location (1 prospective [42] and 2 retrospective studies [21,45]).

Ten potentially relevant ongoing trials were identified, with two (NCT02190903 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 18 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

**Primary Outcome**

**Post-operative delirium**

Fourteen studies reporting unadjusted results are represented in the forest plot (Figure 2), including three of the four RCTs. Based on these 14 studies, only one study found a statistically significant benefit in favour of regional anaesthesia [49] and overall there is no evidence of a benefit of one type of anaesthesia over another. Four further studies not represented in the forest plot (one RCT, [35] two retrospective analyses reported as
abstracts only, [47,50] and one prospective study [31]), also found no significant
differences in delirium based on Abbreviated Mental Test (AMT) or DSM-IV.

None of the RCTs that were quality assessed reported all relevant details (Table 2a).
Details were lacking on the assessment tools used [38] and method of randomisation.
[35,36,38] Blinding of outcome assessment was either not undertaken [38] or unclear,
[36] with only one RCT having a clear statement on blinding. [35] There appeared to be
no loss to follow-up in two RCTs [36,38], but this was unclear for the other RCT. [35]
The RCT by Kamitani was not quality assessed as a full translation was not available.
[37]

The observational studies were generally considered to be at low risk of bias in terms of
patient eligibility, however most had no details on blinding of outcome assessors and
the level of completeness of data was not well described (Table 2b). There were no
details on characteristics of completers compared with those lost to follow up. There
was also a lack of detail on the type of assessment tool used and/or where the cut-off
for a “positive” diagnosis of delirium was.

Most studies did not adjust for potential confounders, but four studies [31,41,49,50],
one of which is also represented in the above plot [49], did present adjusted results.
There was some variation in terms of which confounders were adjusted for (see Table
2b for details). Three studies reported these in full; all included age, gender and ASA
score as well as a range of factors including co-morbidities, surgery type and physical
functioning. None found that type of anaesthesia was predictive of post-operative
delirium.

There was substantial heterogeneity across the 18 studies regarding assessment tools,
assessment time-points and anaesthetic protocol. Many assessment tools were poorly
defined. Only 6 out of 18 studies used either DSM-IV criteria [18,46,50,51] or AMT.
[35,47] Delirium or cognitive impairment was frequently not a primary outcome, but
listed as one of several complications.

**Secondary outcomes**
Mortality

Two RCTs reported mortality (Table 3). One found a small and statistically significant survival benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Ten observational studies reported adjusted results or results based on a matched analysis (Table 3). Two of these [20,62] found a statistically significant benefit in favour of RA for in-hospital mortality. The remaining eight studies found no significant differences. There was a lack of consistency across studies in terms of number and type of variables included in models.

Of the remaining 40 studies (results not shown) reporting unadjusted mortality results only, six [52,56,61,67,68,70] found statistically significant results in favour of RA. The remainder found no statistically significant differences and no consistent trend of benefit.

Overall there is a paucity of good quality evidence evaluating mortality, with only one good quality RCT [38] suggesting benefit from GA at later, but not earlier time points.

Length of hospital stay

Twenty-one [21,36,38,41,44,48,53,54,62,64,65,69,72,74–77,89,91–93] studies reported length of hospital stay; nine could be included in a forest plot (Figure 3, supplementary data). There was no difference in length of hospital stay based on one RCT. [38] The adjusted results, based on three retrospective studies, [21,62,75] showed a slight trend towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,62] the absolute reduction was small (up to around a third of a day). Results from the studies reporting unadjusted results were inconsistent, with three finding no difference, [65,69,74] and two finding a benefit from RA. [76,91]

Of the remaining twelve studies [36,41,44,48,53,54,64,72,77,89,92,100], neither the RCT [36] nor the four prospective studies [41,44,54,92] showed any significant differences. Results from the seven retrospective studies were also inconsistent (three
studies [53,64,77] reported no difference, two studies [48,72] found a statistically significant benefit for RA [72] and one [89] a statistically significant benefit for GA.)

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of ten studies [21,36,44,48,53,64,65,77,89,92] reporting the median, eight studies [21,36,44,53,64,65,77,92] found no statistically significant differences. Two studies found a statistically significant difference in medians favouring RA [48] or GA [89] respectively.

Adverse Events

Twenty-five studies reported adverse events (Table 4, supplementary data). There were many gaps in reporting of POMS adverse events, and it is uncertain whether this reflects non-occurrence or non-reporting of such events. Most commonly reported adverse events were pulmonary (10 studies) [20,21,35,45,49,62,69,89,91] and cardiovascular events (8 studies). [21,35,45,54,62,63,75,89] For pulmonary events, six studies found no statistically significant differences. [35,45,49,69,89,91] Four studies found a statistically significant difference in favour of RA (fewer cases of ventilatory support [62], respiratory failure [20,62] and ‘overall pulmonary’ adverse events [20,48]). There were no differences in occurrences of pneumonia [35,45,49,89] or hypoxia. [69,91] The most commonly reported cardiovascular adverse events were myocardial infarction [45,62,89] and thromboembolic events. [35,54,63,75,89] No differences were found for myocardial infarction. [45,49,62,69,89] Three studies [63,75,89] reported higher incidence of thromboembolic events in GA group.

Nine studies summarised overall adverse events with the majority finding no differences between the types of anaesthesia. Where there was a significant difference, this was in favour in RA (e.g. fewer incidences of ‘all complications’, [48,63] ITU admissions, [62] stroke [62] or requirement for blood transfusion). Three studies [94,96,97] found higher incidences of hypotension in the GA group.
The results are thus suggestive of a lower incidence of post-operative respiratory, cardiac and overall complications in the RA group. However, reporting of adverse events, including methods of ascertainment, was inconsistent and limited.

**Functional outcomes**

Eight studies reported functional outcomes using a variety of outcome measures. A small RCT reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] A further RCT [36] reported a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in the RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005). No differences were found in the non-randomised studies regarding time to ambulation, [98,99] walking speed, [58] time to rise from chair, [41] mean Barthel's score [67] or ambulation at 3, 6 and 12 month post-surgery. [44] Overall results may suggest a small benefit from RA for immediate post-anaesthetic mobilisation. However, the evidence is limited by small sample size, unknown method of outcome assessment and blinding of assessors.

**Discharge location**

Three non-randomised studies described discharge locations of patients following hip fracture. [21,42,45] One study with only 14 patients reported that more patients returned home in the RA group [45]. However, two larger studies [21,97] found no difference in discharge location between GA or RA groups.

**Quality of Life**

There were no studies that evaluated the effect of type of anaesthesia on quality of life in patients after hip fracture surgery.

**Discussion**
For the primary outcome of post-operative delirium, this systematic review did not find any difference between types of anaesthesia. Furthermore, no survival benefit could be demonstrated with either type of anaesthesia up to one year post-operatively. A small number of studies suggested that fewer adverse events might be associated with RA. Similarly some studies were suggestive of a small reduction in hospital stay with RA. Data was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. There were no studies that reported on quality of life after different types of anaesthesia.

This is the most comprehensive and methodologically robust systematic review to date. It includes both RCTs and non-randomised controlled studies, focusing on delirium as a primary outcome as well as synthesising findings for a range of other important outcomes including adverse events. Results for RCTs, non-randomised studies, adjusted and unadjusted results were presented and considered separately. It was anticipated that non-randomised studies, which are more prone to bias, may overestimate effect sizes compared with RCTs. No such trends were observed however, as studies of any design mostly showed no difference in effect.

A sensitive search strategy means it is unlikely that many studies would have been missed. Careful consideration of heterogeneity has meant that no meta-analyses were undertaken, but results were presented in forest plots where possible to show the overall direction of effect and heterogeneity between studies.

Delirium can be diagnosed using the criteria from the DSM-V or the WHO’s ICD-10 classification of diseases. [7,101] However in clinical practice the criteria can be difficult to apply [102] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [103] or 4AT have been advocated as validated screening tools. (4 ‘A’s’ Test) [6,102,104] No consensus exists in the literature as to which tool should be the gold standard. [6,105,106] The accurate assessment of delirium can be affected by the presence of pain and residual drugs in the immediate period following surgery therefore timing of assessment is also important. [107] No significant differences were found for the incidence of post-operative delirium, based on four RCTs and 14 non-
randomised studies but there were significant differences in the assessment tools and the assessment time-points. Most of the RCTs were small and most likely underpowered. In the largest RCT [38] delirium was not a primary outcome and the assessment tool used or the timing of assessments was not reported. The pathophysiology of delirium remains poorly understood but there are a combination of pre-existing and precipitating factors that can pre-dispose the patient to post-operative delirium. [11,108,109] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [110,111] are associated with higher risk of delirium. Precipitating factors can include acute injury such as a hip fracture, malnutrition, electrolyte imbalance and the use of urinary catheter and physical restraints. [111] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [112,113] The studies that adjusted for confounders and reported delirium [31,41,49,50] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. [41,49,50] However, with multifactorial risk factors for delirium, it is difficult to encompass all variables. Other important characteristics such as anaemia, time to surgery, blood loss, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in terms of number and type of variables included in models and the reporting of these, it is not possible to gauge the overall impact that adjusting for confounders may have on the direction of effect.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total number of patients included for the primary outcome) and many of the non-randomised studies did not make any attempts to adjust for potential confounding factors. When confounding variables were considered, this was often done for mortality only. There was significant heterogeneity across studies in study design, population age, comparators, assessment time-points and definition of outcomes (particularly delirium) that precluded quantitative pooling.
Detailed reporting of anaesthetic techniques was suboptimal especially for GA techniques. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium [3,114] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst most studies planned to collect adverse events data, it was unclear whether adverse events were predetermined. Small sample sizes (n<30) and rare occurrences of adverse events means that many studies were likely underpowered. [35,36,45,91]. The style of data reporting in included studies could also lead to over-reporting of complications; for example, a patient could develop pneumonia, which led to respiratory failure and the need for inotropic and ventilatory support and ITU admission. Thus five adverse events would be attributable to a single patient, but this may not be evident from the data. Incidence of intraoperative hypotension was not captured by POM categories, as inotropic support use was not reported. Hypotension can lead to hypoperfusion and organ damage. A recent analysis of data from an audit of outcomes in hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [94,96,97] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [49,63,94,97] also found significantly higher volumes of fluids and blood products transfused in the GA group.

Subgroup analysis was not feasible and no individual studies reported findings for different sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to GA that have not been captured by the evidence presented in this systematic review. Subgroup analysis of specific at risk patients, for example the frail and the very elderly, may suggest a benefit for either regional or general anaesthesia in certain population groups.

Older patients are at high risk of adverse outcomes post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [115] Principles of care for older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [116] Most recently, the European Society of Anaesthestiology consensus-guideline on post-
operative delirium also did not find substantial evidence to recommend a specific type of anaesthetic technique but advocates intraoperative monitoring to avoid swings in blood pressure and excessive depth of anaesthesia. [117] Given the lack of standardised assessment tools of delirium and the paucity of suitably powered, methodologically sound studies, uncertainty remains regarding any potential benefits of certain types of anaesthesia. However, even a modest reduction in adverse events and length of hospital stay could benefit many patients and result in cost savings for health care providers. Future research examining post-operative delirium should include robust assessment and diagnosis of delirium. There is also an urgent need for high quality research comparing anaesthetic techniques that focus on patient-related outcomes such as quality of life and functional outcomes.

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Table 1: Table of characteristics of studies that measured postoperative delirium

| Author             | Year | Country | ASA | Comparison and number of patients | Population                                      | Age, mean age and M/F split | Outcomes measured |
|--------------------|------|---------|-----|-----------------------------------|------------------------------------------------|----------------------------|-------------------|
| **RANDOMISED CONTROLLED TRIALS** |      |         |     |                                   |                                                 |                            |                   |
| Bigler 1985 DENMARK |      |         |     | General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3 | General (n=20) v Spinal (n=20) Patients having acute surgery for hip fracture | Patients above 60 years of age Mean age General: 77.6 years (SEM 2.3) Spinal: 80.1 years (SEM 1.6) M/F: 7/33 | Postoperative mental function Morbidity |
| Casati 2003 ITALY  |      |         |     | General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9 | General (n=15) v Spinal (n=15) Patients undergoing hip fracture repair | Patients over 65 years of age Mean age General: 84 years (range 67-88) Spinal: 84 years (range 71-94) M/F: 2/28 | Hypotension Cognitive dysfunction |
| Kamitani 2003 JAPAN|      |         |     | ASA not reported. Comparable 'physical status' between GA and RA groups | General (n=21) v Spinal (n=19) Patients with femoral neck fracture | Patients aged 70 and over Mean age General: 81.4 (SD 6.2) Spinal: 83. (SD 6.0) M/F: 4/36 | Postoperative delirium |
| Parker & Griffiths 2015 UK |      |         |     | General: ASA Grade 1 or 2: 98 | General (n=164) v Spinal (n=158) Patients with acute hip fracture | Patients over 49 years of age Mean age General: 83.0 years (range 59-99) | Primary: Mortality Secondary: Surgical outcomes |
### Spinal: ASA Grade 1 or 2: 94.9

**PROSPECTIVE STUDIES**

| Study | Design | Groups | Participants | Outcomes |
|-------|--------|--------|--------------|----------|
| Atay 2012 TURKEY | Unable to obtain full translation. | General (n=30) v Spinal (n=40) | Patients with hip fractures | Patients aged 60 years and over Mean age M/F: |
| Bitsch 2006 DENMARK | ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10 | General (n=13) v Regional (n=83) | Hip fracture patients | No age restriction Mean age No significant decline: 81.6 years (range 75-86) Significant decline: 84.5 years (range 81-89) M/F: 28/68 |
| Bjorkelund 2010 SWEDEN | Intervention group (new care plan): ASA 1=17 ASA 2=59 ASA 3=48 ASA 4=7 | General (n=89) v Spinal (n=174) | Patients with hip fractures | Patients aged 65 years and over Mean age Intervention: 81.1 years (SD 7.5) Control: 82.0 years (SD 7.6) M/F: 78/185 |
| Gilbert | General: | General (n=311) v | Patients with an acute | Age 65 years and older | Complications (in-hospital and |

- General complications
- Hospital stay
- Postoperative delirium
- Postoperative cognitive function
- Risk factors for pre, intra and postoperative cognitive dysfunction
- Incidence of Delirium

- Complications (in-hospital and
| Year | Country | ASA 1-2: | ASA 3-4: | Type (n) | Age | General | Spinal | Primary | Secondary |
|------|---------|---------|---------|----------|-----|---------|--------|---------|-----------|
| 2000 | USA     | 105     | 194     | Spinal (n=430) | 65-79 years n=120 | M/F: 156/585 |
|      |         |         |         |          | 80+ years n=191 | |
|      |         |         |         |          | Spinal: 65-79 years n=184 | |
|      |         |         |         |          | 80+ years n=246 | |
| Ilango 2015 | Not reported | General (n=167) v Spinal (n=151) | Hip fracture patients | Age not specified within inclusion criteria | |
| Juliebo 2009 | USA | ASA 1 or 2 = 182 | General (n=20) v Spinal (n=337) | Patients with hip fracture | 85 years (range 82-89) | M/F: 89/229 |
|            | v | | | | No delirium: 82 years (range 77-87) |
| Koval 1999 | USA | General: ASA 1 or 2: 236 | General (n=362) v Spinal (n=280) | Patients who sustained a hip fracture | 65 years of age and older | M/F: 129/513 |
|            | v | AS 3 or 4: 120 | | | Mean age General: 78.5 years | |
|            | v | Spinal: ASA 1 or 2: 131 | | | Spinal: 81.0 years | |
|            | v | AS 3 or 4: 137 | | | | |

**RETROSPECTIVE STUDIES**
| Author | Year | Country | Group | Age Criteria | Postoperative Complications | Intraoperative Variables | Perioperative Complications |
|--------|------|---------|-------|--------------|----------------------------|-------------------------|----------------------------|
| Bellelli 2013 | ITALY | ITALY | General v Spinal v Peripheral nerve block | Patients undergoing hip fracture surgery | Patients aged 65 years and older | Postoperative delirium |  |
| Kim 2013 | KOREA | KOREA | General (n=246) v Spinal (n=249) v Epidural (n=11) | Hip fracture surgery patients | Patients aged 60 years and over | 30 day postoperative complications |  |
| Konttinen 2006 | FINLAND | FINLAND | General (n=3) v Spinal (n=11, single shot: 5, continuous: 6) | Patients undergoing major emergency surgery | Patients aged 100 years and over | Intraoperative variables |  |
| Luger 2014 | AUSTRIA | AUSTRIA | Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6 | Patients scheduled for acute hip fracture surgery | Patients aged 80 years of age and older | Cognitive decline |  |
| **Michael** 2014 UK Abstract | Not reported | General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia) | Hip fracture patients | Patients aged 60-100 years | Pre and post-operative cognitive function |
|---|---|---|---|---|---|
| | | | Age | 60-70 years n=50 70-80 years n=169 80-90 years n=338 90-100 years n=147 |
| | | | M/F: 178/526 | |
| **O’Hara 2000 USA** | General: ASA 1 or 2: 1698 ASA 3: 3666 ASA 4 or 5: 618  Regional: ASA 1 or 2: 560 ASA 3: 2097 ASA 4 or 5: 438 | General (n=6206) v Regional (n=3219, spinal n=3078 and epidural n=141) | Hip fracture patients | Patients 60 years of age or older | |
| | | | Age | General: 60-69 years n=910 70-79 years n=1918 80-89 years n=2602 90+ years n=776  Regional: 60-69 years n=325 70-79 years n=881 80-89 years n=1452 90+ years n=561 |
| | | | M/F: 2010/7415 | |
| **Shih 2010 TAIWAN** | General: ASA 2: 47 ASA 3: 115 ASA 4: 1 Spinal: ASA 2: 45 ASA 3: 120 ASA 4: 2 | General (n=167) v Spinal (n=168) | Patients undergoing hip fracture repair | Patients aged 80 and over | Postoperative morbidity - Postoperative mortality - Pre and intraoperative variables |
| | | | Mean age | General: 83.96 years (SD 3.71) Spinal: 84.93 years (SD 4.04) |
| | | | M/F: 189/146 | |
### Table 2a: Quality assessment of RCT studies reporting delirium

AMT is Abbreviated mental test  
CAM is Confusion assessment method  
DRS is Delirium Rating Scale  
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition  
MMSE is Mini mental state examination

| Study                    | Randomisation | Concealment of allocation | Similarity at baseline | Blinding of outcome assessor | Incomplete outcome data (for outcome of delirium) | Validity of assessment tool | Assessmen tool specific for delirium | Selective reporting |
|--------------------------|---------------|---------------------------|------------------------|------------------------------|-----------------------------------------------|-----------------------------|-----------------------------------|------------------|
| **Parker & Griffiths 2015** N=322 | UNCLEAR       | LOW                       | Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group). | HIGH | LOW | Unclear-no details | Unclear | UNCLEAR |
|                          |               |                           |                        |                              |                                               |                             |                                   |                   |
|                          | Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial. |                  |                        |                              |                                               |                             |                                   |                   |
|                          |               |                           |                        |                              |                                               |                             |                                   | Insufficient information to permit judgement. |
| **Casati 2003** N=30    | UNCLEAR       | LOW                       | Groups similar for all baseline characteristics measured. | UN clearing | LOW | MMSE for all 30 patients at 1 and 7 days. | No | UNCLEAR |
|                          |               |                           |                        |                              |                                               |                             |                                   | Insufficient information to permit judgement. |
|                          | Using a sealed envelope technique, patients were randomly allocated... |                  |                        |                              |                                               |                             |                                   |                   |
| **Bigler1985** N=40     | UNCLEAR       | UN CLEAR                  | Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group. | LOW    | UN CLEAR | AMT unaware of anaesthesia given | No | UNCLEAR |
|                          |               |                           |                        |                              |                                               |                             |                                   | Insufficient information to permit judgement. |

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.
### Table 2b: Quality assessment of observational studies reporting delirium

AMT is Abbreviated mental test  
CAM is Confusion assessment method  
DRS is Delirium Rating Scale  
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition  
MMSE is Mini mental state examination

| Study                  | Eligibility criteria                                      | Confounders Low risk                      | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------------------|-----------------------------------------------------------|-------------------------------------------|-------------------------------|---------------------------------|---------------------------|-------------------------------|
| **Atay 2010**          | Low risk for adjusted data                                | Likely LOW for adjusted data              | LOW                           | DSM-IV, MMSE and DRS           | Yes                       |                                |
| **(Abstract only in English)** | Multivariate analysis-variables not stated in abstract.  |                                            |                               |                                 |                           |                                |
| **Belleli 2013**       | LOW            | HIGH for unadjusted data & LOW for adjusted data | UNCLEAR                       | LOW                            | Yes                       | UNCLEAR                       |
| **(Abstract)**         | patients aged > 65 years admitted to one orthogeriatric unit between 2007 and 2011. | Patients with incomplete data in medical records were excluded from this study. Proportion not stated. |                                | DSM-IV-TR criteria           |                          |                                |
| **RETRORSPETIVE**      | UNCLEAR        | BASELINE CHARACTERISTICS not presented for anaesthesia groups, but multivariate analysis for confounders (age, gender, Charlson Comorbidity Index, ASA score, pre-fracture disability in Activities of Daily Living (Katz’s ADL index), and pre-fracture dementia) | No details                    |                                 |                           | Patients with incomplete data in medical records were excluded from this study. Proportion not stated. |
| **Bitsch 2006**        | UNCLEAR        | HIGH                                      | UNCLEAR                       | LOW-good validity for cognitive function | No                       | HIGH                          |
| **PROSPECTIVE**        | Consecutive patients but large number excluded and unclear if similar characteristics to included | No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses. | No details                    | MMSE                            |                           | 12/96 (12.5%) and 35/96 (36%) patients not available for testing on day 4 and 7 respectively. Nursing home patients considered stable and those achieving independent ambulation discharged earlier. |
| Study                | Eligibility criteria | Confounders | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|---------------------|----------------------|-------------|-----------------------------|----------------------------------|---------------------------|--------------------------------|
| Björkelund 2010     | LOW                  | HIGH        | UNCLEAR                     | LOW (Organic Brain Syndrome Scale and DSM-IV criteria) | No for Organic Brain Syndrome Scale | LOW Appears to be no loss to follow up from included patients for delirium assessment |
|                     | PROSPECTIVE          |             |                             |                                  |                           |                                |
|                     | Consecutive patients included |             |                             |                                  |                           |                                |
|                     |                      |             |                             |                                  |                           |                                |
| Gilbert 2000        | LOW                  | HIGH        | UNCLEAR                     | LOW (MMSE) HIGH ("mental confusion") | Unclear ("mental confusion") No (MMSE) | UNCLEAR |
|                     | PROSPECTIVE          |             |                             |                                  |                           |                                |
|                     | Patients given general and spinal were drawn from the same population |             |                             |                                  |                           |                                |
|                     |                      |             |                             |                                  |                           |                                |
| Ilango 2015         | LOW                  | HIGH        | UNCLEAR                     | Subjective method ("clinical judgement") and several scales; cut-off unclear. | Unclear | UNCLEAR |
|                     | PROSPECTIVE          |             |                             |                                  |                           |                                |
|                     | All hip fracture patients admitted over a year |             |                             |                                  |                           |                                |
|                     |                      |             |                             |                                  |                           |                                |
| Juliebo 2009        | LOW                  | HIGH        | UNCLEAR                     | Low CAM | Yes | HIGH |
|                     | PROSPECTIVE          |             |                             |                                  |                           |                                |
|                     | All eligible hip fracture patients September 2005 to December 2006. |             |                             |                                  |                           |                                |
|                     |                      |             |                             |                                  |                           |                                |

- **Björkelund 2010**: No baseline characteristics for groups according to type of anaesthetic; no adjusted analyses.
- **Gilbert 2000**: Appears to be some baseline imbalances between general and regional groups, but multivariate analyses for all outcomes. Variables were age, sex, race, comorbidities, pre-fracture physical function, ASA score, fracture type, surgical procedure and physiologic status.
- **Ilango 2015**: Subjective method ("clinical judgement") and several scales; cut-off unclear.
- **Juliebo 2009**: No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part.

Pre-operative delirium an exclusion criterion; 127/364 (35%) included not assessed pre-operatively and excluded. No details on their characteristics.
| Study          | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|---------------|----------------------|----------------------|-------------------------------|----------------------------------|---------------------------|--------------------------------|
| Kim 2013      | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | Yes                       | LOW                           |
| RETROSPECTIVE | Consecutive sample of hip fracture patients | No adjusted analyses including type of anaesthesia. No details on similarity of baseline characteristics for groups. | No details | DSM-IV criteria | | Appears to be no missing data |
| Kontinenen 2006 | LOW                  | HIGH                 | UNCLEAR                       | UNCLEAR                         | UNCLEAR                   | Unclear                        |
| RETROSPECTIVE | All patients over 100 years old undergoing emergency Surgery in one hospital | No adjusted analyses. | No details | Not clearly defined | | No details on missing data/exclusions. |
| Koval 1999    | LOW                  | HIGH                 | UNCLEAR                       | UNCLEAR                         | UNCLEAR                   | Unclear                        |
| PROSPECTIVE   | Patients with hip fracture admitted to one hospital between 1987 and 95. Patient excluded if certain characteristics meant type of anaesthetic was predetermined. | Some imbalances in baseline characteristics. Adjustment for covariates described but results presented appear to be unadjusted. | No details | Not clearly defined | | 4.4% of patients lost to follow-up. No further details |
| Luger 2014    | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | Yes (DSM-IV)              | HIGH                           |
| RETROSPECTIVE | Patients scheduled for acute hip fracture surgery at Innsbruck Medical University between 2005 and 2007 | No details on baseline characteristics between groups. No adjusted analyses. | No details | "Unspecified cognitive dysfunction behaviour" and DSM-IV | | 82/411 (20%) excluded due to incomplete records. Unclear if excluded had different characteristics to those included |
| Michael 2014  | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | Yes                       | UNCLEAR                        |
| (Abstract)    | Consecutive patients | No details on baseline characteristics between groups. No adjusted analyses. | No details | AMT | | 34/738 (5%) excluded retrospectively. No reasons for exclusions. |
| Study       | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------|----------------------|----------------------|-------------------------------|----------------------------------|---------------------------|--------------------------------|
| O’Hara 2000 | LOW                  | HIGH for unadjusted data, LOW for adjusted data | UNCLEAR                      | UNCLEAR                          | Unclear                   | UNCLEAR                        |
| RETROSPECTIVE | Consecutive patients from 20 hospitals | Appear to be some baseline imbalances between groups, but multivariate analyses. Variables were gender, history of cardiovascular disease, history of stroke, abnormal preoperative chest radiograph, type of surgical repair, age, hospital, and ASA score. | No details                     | Not clearly defined            | 9425/9598 < 2% missing        |
| Shih 2010   | LOW                  | HIGH                 | UNCLEAR                       | UNCLEAR                          | Unclear                   | LOW                            |
| RETROSPECTIVE | Octogenarian patients undergoing hip fracture repair in one centre between 2002 and 2006. | Some baseline imbalances between groups; no adjusted analyses for delirium (only for “morbidity”) generally. | No details                     | Not clearly defined            | Appears to be no missing data from those patients included. |

NB Quality assessment was not performed for Atay [31] as a full translation was not available.
Table 3 Mortality results

| Study               | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI) | Adjusted/matched OR or RR (95% CI) | Note                                                                 |
|---------------------|------------|---------------------|---------------------|------------------------------|------------------------------------|----------------------------------------------------------------------|
| **RCTs**            |            |                     |                     |                              |                                    |                                                                      |
| Bigler 1985         | In-hospital| 1/19                | 1/19                | RR=1.00 (0.07, 14.6)         |                                    | No statistically significant difference in in-hospital mortality.    |
| Parker & Griffiths 2015 | 30 day    | 8/156               | 5/153               | RR=1.54 (0.52, 4.58)         |                                    | No statistically significant difference in mortality at 30 or 90 days. |
| Parker & Griffiths 2015 | 90 day    | 12/152              | 12/146              | RR=0.96 (0.45, 2.07)         |                                    | Statistically significant difference in mortality at 120 days and 1 year in favour of GA |
| Parker & Griffiths 2015 | 120 day   | 12/152              | 15/143              | RR=0.77 (0.61, 0.91)         |                                    |                                                                      |
| Parker & Griffiths 2015 | 1 year    | 19/145              | 32/126              | RR=0.57 (0.34, 0.96)         |                                    |                                                                      |
| **Prospective cohort** |          |                     |                     |                              |                                    |                                                                      |
| Withey 1995         | 1 year     | Total only reported: 303 | Total only reported: 161 | Not reported. | OR 1.28 (0.76, 2.14) | No statistically significant difference in mortality (adjusted data). |
| Zhao 2015           | Unknown    | 65/166              | 22/238              | Not reported. | OR 0.687 (0.248, 1.906) | No statistically significant difference in mortality (adjusted data). |
| **Retrospective cohort** |          |                     |                     |                              |                                    |                                                                      |
| Chu 2015            | In-hospital| 1363/50681          | 1107/50937          | Not reported. | OR 1.24 (1.15, 1.35) | Statistically significant difference in mortality (adjusted data) in favour of RA. |
| Neuman 2012         | In-hospital| 325/12579           | 110/5144            | Not reported. | OR 0.710 (0.541, 0.932) | Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA). |
| Paterno 2014        | In-hospital| 1477/66345          | 144/6939            | RR 0.94 (0.79 to 1.11)       | RR 0.93 (0.78 to 1.11) | No statistically significant difference in mortality (adjusted or unadjusted). |
| O’Hara 2000         | 7 day      | 82/6124             | 53/3076             | OR 0.80 (0.56-1.13)          | OR 0.90 (0.59-1.39) | No statistically significant difference in mortality (adjusted or unadjusted). |
| Basques 2015        | 30 day     | 450/6803            | 166/2423            | 0.97 (0.81 to 1.17)          | OR 0.98 (0.82 to 1.20) | No statistically significant difference in mortality (adjusted or unadjusted). |
| O’Hara 2000         | 30 day     | 272/5934            | 174/2955            | OR 0.80 (0.66-0.97)          | OR 1.08 (0.84-1.38) | No statistically significant difference in mortality (adjusted or unadjusted). |
| Seitz 2014          | 30 day     | 1044/7774           | 1450/10705          | RR 0.99 (0.92, 1.07) (calculated based on raw data) | RR 1.04 (0.94, 1.15) (calculated based on raw data) | No statistically significant difference in 30 day mortality (matched or unmatched). |
| Study          | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI) | Adjusted/matched OR or RR (95% CI) | Note                                                                 |
|---------------|------------|---------------------|---------------------|-----------------------------|------------------------------------|----------------------------------------------------------------------|
| Whiting 2015  | 30 day     | Total only stated: 5840 | Total only stated: 1924 | Not reported.               | Spinal and regional nerve blocks  | OR 1.18 (0.91, 1.53) Spinal only OR 1.20 (0.92–1.56) Regional only OR 1.22 (0.54–2.76) No statistically significant difference in 30 day mortality (adjusted data). |

**Note:** based on raw data reported. OR is odds ratio; RR is relative risk.
Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

| POMS categories | Study          | Adverse event description | GA     | RA     | Summary statistic*/p-value |
|-----------------|----------------|---------------------------|--------|--------|---------------------------|
| Pulmonary       | Basques 2015   | Ventilatory support       | 58/7253 (0.8%) | 13/2589 (0.5%) | NR                        |
|                 |                | Pneumonia                 | 261/7253 (3.6%) | 108/2589 (4.2%) | NR                        |
|                 | Bigler 1985    | Pneumonia                 | 2/20   | 1/20   | NR                        |
|                 | Chu 2015       | Respiratory Failure       | 868/52043 (1.61%) | 328/52044 (0.63%) | OR 2.71 (95%CI 2.38 to 3.01), p<0.001, Favours RA |
|                 |                | Ventilatory support       | 4008/52043 (7.70%) | 338/52044 (1.44%) | OR 6.08 (95%CI 5.59 to 6.61), p<0.001, Favours RA |
|                 | Konttinen 2006 | Pneumonia                 | 0/3    | 2/11   | NR                        |
|                 | Le Liu 2014    | Overall pulmonary         | 18/172 (25%) | 27/145 (25.5%) | P=0.934 NS                |
|                 |                | Hypoxia                   | 19/72 (26.4%) | 23/145 (15.9%) | P=0.065 NS                |
|                 | Le Wendling 2012 | Overall pulmonary     | 17/235 (6%) | 1/73 (1%) | OR 2.2 (95%CI 0.7 to 7.2), P=0.0841, Favours RA |
|                 | Naja 2000      | Hypoxia                   | 2/30 (6%) | 0/30 (0%) | NR                        |
|                 | Neuman 2012    | Overall pulmonary         | 1030/12904 (8.1%) | 359/5254 (6.8%) | P=0.005, Favours RA      |
|                 |                | Respiratory Failure       | 1040/12904 (5%) | 178/5254 (3.4%) | P<0.0001, Favours RA      |
| Study          | Condition                | Event | Controls | OR (95% CI) | P-value | Conclusion        |
|---------------|--------------------------|-------|----------|-------------|---------|-------------------|
| O'Hara 2000   | Pneumonia                | 174/6206 (2.8%) | 84/3219 (2.6%) | OR 1.21 (0.87 to 1.68) | NS      |                   |
| Shih 2010     | Overall pulmonary        | 11/167 (6.6%) | 3/168 (1.8%) | P<0.03 | Favours RA        |
| Cardiovascular| Basques 2015 Myocardial infarction | 137/7253 (1.9%) | 49/2859 (1.9%) | NR      |                   |
| Cardiovascular| Bigler 1985 Cardiovascular decompensation | 1/20 | 1/20 | NR |                   |
| Cardiovascular| Bigler 1985 Pulmonary embolism | 1/20 | 1/20 | NR |                   |
| Chu 2015      | Myocardial infarction    | 188/52043 (0.36%) | 169/52044 (0.32%) | OR 1.11 (0.90 to 1.37), p=0.31 | NS |                   |
| Fields 2015   | Thromboembolism          | 1.64% | 0.72% | P=0.004 | Favours RA | |
| Konttinen 2006| Myocardial infarction    | 0/3 | 1/11 | NR | |
| Le Wendling 2012| All cardiovascular complications | NR | NR | OR 1.7 (0.4 to 6.3) | NS | |
| Seitz 2014    | Deep vein thrombosis     | 47/8818 (0.5%) | 41/12155 (0.3%) | P=0.03 | NS when matched | |
|               | Pulmonary Embolism       | 100/8818 (1.1%) | 93/12155 (0.8%) | P=0.006 | NS when matched | |
| Sutcliffe 1994| Deep vein thrombosis     | 16/950 (1.7%) | 14/383 (3.7%) | P<0.05 | NS | |
|               | Pulmonary Embolism       | NR | NR | NS | |
| Infectious    | Bigler 1985 Wound infection | 1/20 | 0/20 | NR | |
| Fields 2015   | Urinary Tract infection  | 5.76% | 8.87% | P<0.0001 | Favours GA |
| Author          | Study Type            | Complication       | Basques 2015 | Basques 2015 | Basques 2015 | NS |
|-----------------|-----------------------|--------------------|--------------|--------------|--------------|----|
| Rashid 2013     | Urinary Tract infection | NR                | NR           | NR           | NS           |    |
| Basques 2015    | Wound infection       | 94/7253 (1.3%)     | 39/2589 (1.5%) | NS           |    |
| Renal Basques 2015 | Acute Renal Failure | 29/7253 (0.4%)     | 10/2589 (0.4%) | NS           |    |
| Bigler 1985     | Urinary retention     | 4/20               | 5/20         | NS           |    |
| Chu 2015        | Acute Renal Failure   | 78/52043 (0.15%)   | 56/52044 (0.11%) | P=0.06 NS   |    |
| Naja 2000       | Acute Renal Failure   | 2/30 (6%)          | 0/30 (0%)    | NS           |    |
| Overall complications | Gilbert 2000 | Serious medical complications | 55/311 (17.7%) | 79/430 (18.4%) | OR 0.92 (95%CI 0.61 to 1.4) NS |
| Giblet 2000     | Fewer medical complications | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95%CI 0.90 to 1.82) NS |
| Whiting 2015    | Surgical complications | 15/311 (4.8%)    | 19/430 (4.4%) | OR 1.08 (95%CI 0.65 to 1.21) NS |
| Major complications | NR               | NR                | OR 1.43 (95%CI 1.16-1.77) NS |
| Whiting 2015    | Minor complications   | NR                | NR           | OR 1.02 (95%CI 0.82 to 1.26) NS |
| Fields 2015     | All complications     | NR                | NR           | OR 1.24 (95%CI 1.05 to 1.48) NS |
| All complications | 2357/4813 (48.97%) | 830/1815 (45.75%) | OR 1.29 (95%CI 1.13 to 1.47), p=0.0002 |
| Hekimoglu Sahin 2012 | All complications | NR                | NR           | NS           |    |
| Ilango 2015     | All complications     | NR                | NR           | NS           |    |
| Koval 1999      | All complications     | 41/362 (11.3%)    | 32/280 (11.4%) | NS           |    |
| Le Liu 2014     | All complications     | 17/72 (23.6%)     | 50/145 (34.5%) | P=0.165 NS   |    |
| Study          | Type                  | Adjusted | Control | OR (95% CI)   | Significance | Conclusion   |
|---------------|-----------------------|----------|---------|---------------|--------------|--------------|
| Le Wendling 2012 | All complications | NR       | NR      | OR 1.7 (0.7 to 4.1) NS |             |              |
| Radcliffe 2013 | All complications    | 22%      | 19%     |               | Log regression model p=0.002 | Favours RA   |
| Shih 2010     | All complications    | 21/167 (12.6%) | 9/168 (5.4%) | P<0.02 |              | Favours RA   |
| Chu 2015      | ITU admissions       | 5743/520 (11.03%) | 3205/520 (6.16%) | OR 1.95 (1.87 to 2.05), p<0.001 |              | Favours RA   |
| Specific complications | Chu 2015 | ITU stay >3 days | 1206/520 (2.32%) | 411/5204 (0.79%) | P<0.001 |              | Favours RA   |
| Baumgarten 2012 | Pressure ulcers     | 10/328 (3.0%) | 18/313 (5.8%) | OR 1.3 (1.0-1.6) |              | Favours GA   |
| Casati 2003   | Hypotension requiring crystalloid infusion | 12/15 (80%) | 7/15 (46%) | P=0.05 NS |              |              |
| Maia 2014     | Intraoperative hypotension | 25/50 (83%) | 80/173 (68%) | P=0.014 |              | Favours RA   |
| Minville 2008 | Intraoperative hypotension | 35/42 (83%) | 74/109 (68%) | NS |              |              |
| Messina 2013  | Haemodynamic changes first 10min | Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA | | Favours RA |              |              |
| Basques 2015  | Blood transfusion    | 2843/7253 (39.2%) | 851/2589 (32.9%) | Matched OR 1.34 (1.22 to 1.49), p<0.001 |              | Favours RA   |
| Fields 2015   | Blood transfusion    | 45.49%   | 39.34%  | P<0.0001 | |              |
|                      |                  |                  |                |
|----------------------|------------------|------------------|----------------|
| Minville 2008        | Blood transfusion| 23%              | 4%             |
|                      |                  |                  | P<0.05         |
|                      |                  |                  | Favours RA     |
| Shih 2010            | Blood loss       | Median 250 (0-1600) ml | Median 200 (0-1200) ml | P=0.01 |
|                      |                  |                  | Favours RA     |
| Chu 2015             | Stroke           | 840/5204 3 (1.61%) | 717/5204 4 (1.38%) | OR 1.18 (95%CI 1.07 to 1.31), p=0.001 |
|                      |                  |                  | Favours RA     |
| Le Liu 2014          | Stroke           | 5/72 (5.9%)      | 4/145 (2.8%)   | P=0.145 NS |

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported
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Figure Legends

Figure 1: PRISMA Flow Diagram. Legend: The PRISMA diagram details our search and selection process applied during the review.

Figure 2: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI=confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

Figure 3: Forest plot of studies reporting length of hospital stay. WMD=weighted mean difference, CI=confidence interval
| Study                  | Assessment tool | Time-point                      | Data GA | Data RA | RR (95% CI) |
|-----------------------|-----------------|--------------------------------|---------|---------|-------------|
| RCT                   | Unknown         | Unknown                         | 0.104/  | 0.108/  | 0.54 (0.20, 1.44) |
| Cassell 2000          | MMSE 2 points   | Day 1 post-op                   | 0.110/  | 0.118/  | 1.55 (0.21, 11.11) |
| Cassell 2000          | MMSE 2 points   | Day 7 post-op                   | 0.015/  | 0.019/  | 1.00 (0.30, 3.50) |
| Kamath 2003           | CAM             | Day 0+                          | 0.221/  | 0.232/  | 2.02 (0.22, 19.02) |
| Kamath 2003           | CAM             | Day 1-2                         | 0.081/  | 0.118/  | 1.71 (0.12, 11.82) |
| Kamath 2003           | CAM             | Day 2-8                         | 0.221/  | 0.217/  | 2.32 (1.12, 4.79) |
| Prospective           | MIVS 2 points   | Day 2-7                         | 0.13/   | 0.28/   | 1.23 (0.29, 9.23) |
| Ethoch 2000           | MMSE 2 points   | Day 2-7                         | 0.13/   | 0.185/  | 2.16 (0.32, 3.53) |
| Bjorklund 2015 (MIVS)| OSAS + CMIVS    | 8 hours minimum post-op         | 0.229/  | 0.238/  | 0.77 (0.33, 1.80) |
| Bjorklund 2015 (MIVS)| OSAS + CMIVS    | 8 hours minimum post-op         | 0.70/   | 0.282/  | 0.17 (0.05, 0.51) |
| Gilbert 2000          | Unspecified     | Typically 8-10 days post-op     | 0.230/  | 0.289/  | 1.10 (0.32, 3.73) |
| Meng 2015             | GCS + BCS + EDCS| Early post-op robbery          | 0.14/   | 0.15/   | 0.85 (0.23, 3.33) |
| Jutaka 2005           | CAM             | Up to 5 days post-op            | 0.11/   | 0.41/   | 4.90 (1.19, 17.9) |
| Kves 2008             | Unspecified     | Not specified                   | 0.2/    | 0.25/   | 1.15 (0.30, 4.62) |
| Retrospective         | ESMIV            | Within 30 days                  | 0.3145/ | 0.25/   | 1.07 (0.72, 1.63) |
| Kontinen 2008         | CAM             | Within 5 days post-op           | 0.1/    | 0.1/    | 0.85 (0.35, 2.03) |
| Lugher 2014           | ESMIV           | Not specified                   | 0.11/   | 0.12/   | 1.17 (0.86, 1.60) |
| Lugher 2014           | ESMIV or UCES   | Not specified                   | 0.11/   | 0.12/   | 1.17 (0.86, 1.60) |
| O’Hare 2003           | Unspecified     | Within 7 days                   | 0.015/  | 0.03/   | 0.21 (0.03, 1.06) |
| 3Mh 2010              | Unspecified     | Below discharge                 | 0.18/   | 0.18/   | 0.94 (0.77, 1.16) |

RR>1 favours regional anaesthesia

73x58mm (300 x 300 DPI)
### Study Summary

| Study          | Study Type | Anaesthesia Type | No. GA | No. RA | WMD (95% CI) |
|----------------|------------|------------------|--------|--------|--------------|
| NCT 021       | RCT        | Spinal           | 154    | 154    | 0.00 (-0.26, 0.26) |
| Asurmet       | Retrospective | Nerve block    | 6284   | 6264   | 0.02 (0.24, 0.42)  |
| Lou-Van Taming 2012 | Retrospective | Local  | 235    | 73     | 0.19 (0.11, 0.27)  |
| Swa 2014      | Retrospective | Regional        | 6135   | 6155   | 0.16 (0.08, 0.28)  |
| Unpublished   | Prospective | Combined Spinal/ PNB | 58    | 50     | 0.45 (0.57, 1.23)  |
| Makroughi Sahi 2012 | Retrospective | Spinal & Epidural | 67    | 111    | -0.28 (-2.20, 1.59) |
| Le Liu 2014    | Retrospective | Peripheral nerve blocks | 77    | 143    | 0.07 (0.10, 0.29)  |
| Rashid 2013   | Retrospective | Regional        | 167    | 97     | 0.73 (0.18, 1.60)  |
| Syrvosa 1985  | Retrospective | Epidural        | 261    | 142    | 0.20 (0.21, 1.19)  |

**WMD >0 favours regional anaesthesia**

67x54mm (300 x 300 DPI)
Appendix A: Example of search strategy

1 exp Hip fracture/
2 hip fracture.mp.
3 (fracture$ adj2 (hip or femur$ or femor$)).tw.
4 or/1-3
5 exp an$esthesia/
6 an$esthesia.mp.
7 (anesthe$ or anaesthe$).tw.
8 an$ethetic.mp.
9 exp anesthetics/
10 exp general an$esthesia/
11 general an$esthesia.mp.
12 Anesthesia/ (43366)
13 exp Anesthesia, General/
14 general an$esthesia.mp.
15 sedation.mp. (28516)
16 exp regional an$esthesia/
17 regional an$esthesia.mp.
18 peripheral an$esthesia.mp.
19 central blockade.mp.
20 central block.mp.
21 exp spinal an$esthesia/
22 spinal an$esthesia.mp.
23 exp epidural an$esthesia/
24 epidural an$esthesia.mp.
25 exp local an$esthesia/
26 local an$esthesia.mp.
27 infiltrative an$esthesia.mp.
28 peripheral nerve block.mp.
29 intravenous regional an$esthesia.mp.
30 systemic local an$esthesia.mp.
31 exp nerve block$/
32 nerve block$.mp.
33 neuroaxial blockade.mp.
34 Anesthesia/ or exp Anesthesia, Intravenous/
35 exp inhalation an$esthesia/
36 inhalation an$esthesia.mp.
37 or/5-36
38 4 and 37
### Appendix B: Table of eligible on-going studies

| Title                                                                 | ID            | Comparison | Status                                      | Design                        | Contact                          | Country   |
|-----------------------------------------------------------------------|---------------|------------|---------------------------------------------|-------------------------------|----------------------------------|-----------|
| Variations in Anaesthesia care for hip fracture surgery                | NCT02787031   | General v Neuraxial                          | Recruitment completed but no results available | Retrospective observational cohort | Ottawa Hospital Research Institute | Canada    |
| A trial to assess the risk of delirium in older adults undergoing hip fracture surgery with spinal or general anaesthesia | NCT02190903   | General v Spinal                             | Recruitment completed but no results available | Open label randomised trial     | Mark D Neuman                    | USA       |
| Regional versus general anaesthesia for promoting independence after hip fracture | NCT02507505   | General v Regional                           | Recruiting patients            | Double blind randomised trial   | Mark Powell/Mark Neuman          | USA       |
| Effect of anaesthesia on post-operative delirium in elderly patients undergoing | NCT02213380   | General v Regional                           | Recruiting patients            | Open label randomised controlled trial | Ting Li/Sishi Chen                | China     |
| Study Title                                                                 | NCT Number     | Type of Anaesthesia | Study Design                        | Country        |
|----------------------------------------------------------------------------|----------------|---------------------|-------------------------------------|----------------|
| The safety of anaesthesia management for traumatic hip surgery in elderly  | NCT02692989   | General v Regional  | Ongoing, but not recruiting patients | Jordan         |
| Anaesthesia and post-operative mortality after proximal femur fractures    | NCT02406300   | Peripheral nerve block/General v Subarachnoid anaesthesia | Enrolling patients by invite only   | Portugal       |
| Effect of anaesthesia in fracture healing                                   | NCT02621255   | General v Regional  | Recruiting patients                 | Turkey         |
| Mortality following surgery for proximal femoral fractures                  | NCT01807039   | General vs. Subarachnoid anaesthesia | Study has been completed            | Czech Republic |
| Practice survey on femoral neck fractures and the incidence of type of anaesthesia on | NCT02198820 | General v Regional  | **WITHDRAWN**                       | Belgium        |
| patient outcome | ICTRP | General v Spinal | Completed | Double blind randomised trial | Mohammad Haghighi | Iran |
|----------------|-------|------------------|-----------|-----------------------------|--------------------|------|
| Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery | IRCT201308316280N4 | Completed | Double blind randomised trial | Mohammad Haghighi | Iran |
| Section/topic       | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|--------------------|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**          |   |                                                                                                                                                                                                                  |                   |
| Title              | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                                | 1                 |
| **ABSTRACT**       |   |                                                                                                                                                                                                                  |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2,3               |
| **INTRODUCTION**   |   |                                                                                                                                                                                                                  |                   |
| Rationale          | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                     | 5,6               |
| Objectives         | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                       | 6                 |
| **METHODS**        |   |                                                                                                                                                                                                                  |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                                     | 6                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                                              | 6                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                                           | 6                 |
| Search             | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                       | Appendix A       |
| Study selection    | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                              | 7                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                                | 7                 |
| Data items         | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                                   | 8                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 23-27             |
| Summary measures   | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                       | 8                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.                                                                   | 8                 |
# PRISMA 2009 Checklist

## Section/topic | # | Checklist item | Reported on page #
--- | --- | --- | ---
Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 23-27
Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | NA

## RESULTS

### Study selection

17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8, Figure 1

### Study characteristics

18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 18-22

### Risk of bias within studies

19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 23-27

### Results of individual studies

20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 2a/b, 3, 4, Figure 2, 3

### Synthesis of results

21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | NA

### Risk of bias across studies

22 | Present results of any assessment of risk of bias across studies (see Item 15). | 23-27

### Additional analysis

23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | NA

## DISCUSSION

### Summary of evidence

24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13,14

### Limitations

25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15, 16

### Conclusions

26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16

## FUNDING

### Funding

27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 16

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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| Primary Subject Heading | Anaesthesia                               |
| Secondary Subject Heading | Geriatric medicine                       |
| Keywords         | General anaesthesia, Regional anaesthesia, Hip fracture, Delirium & cognitive disorders < PSYCHIATRY, Systematic review |

Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Figure 1 updated.jpg
The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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Word Count
Abstract 292
Main manuscript 3681
ABSTRACT

Objective
Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium. This systematic review will investigate the impact of anaesthetic technique on post-operative delirium. Other outcomes included mortality, length of stay, complications and functional outcomes.

Design
Systematic review of randomised controlled trials and non-randomised controlled studies.

Data Sources
Bibliographic databases were searched from inception to June 2018. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers were searched to identify on-going trials.

Eligibility criteria
Studies were eligible if general and regional anaesthesia were compared in patients (aged 60 and over) undergoing hip fracture surgery, reporting primary outcome of post-operative delirium and secondary outcomes of mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life. Exclusion criteria were anaesthetic technique or drug not considered current standard practice; patients undergoing hip fracture surgery alongside other surgery and uncontrolled studies.

Results
One hundred and four studies were included. There was no evidence to suggest that anaesthesia type influences post-operative delirium or mortality. Some studies
suggested a small reduction in length of hospital stay with regional anaesthesia. There
was some evidence to suggest that respiratory complications and intraoperative
hypotension were more common with general anaesthesia. Heterogeneity precluded
meta-analysis. All findings were described narratively and data were presented where
possible in forest plots for illustrative purposes.

Conclusions
Whilst there was no evidence to suggest that anaesthesia types influences post-
operative delirium, the evidence base is lacking. There is a need to ascertain the impact
of type of anaesthesia on outcomes with an adequately powered, methodological
rigorous study.

This review is registered with PROSPERO (CRD42015020166).
STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review provides an update to evidence that examines whether the type of anaesthesia affects the development of post-operative delirium in patients with hip fractures.
- The review included randomised and non-randomised studies that included one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.
- Other outcomes were mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
INTRODUCTION

There are an estimated 70 000-75 000 hip fractures in the UK each year with an annual cost of £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current illness [3] and are at risk of mortality and significant morbidity. In 2014, the National Hip Fracture Database reported 30-day mortality as 7.5%. [4] Following surgery, adverse outcomes can include delirium, myocardial infarction, pneumonia, and cerebrovascular accident. [5]

Delirium is a common neuropsychiatric syndrome defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as the disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day. [6,7] Post-operative delirium has been reported to affect between 32%-53.3% of patients and is associated with prolonged hospital stay, discharge to care homes, difficulty in regaining function in activities of daily living and increased risk of development of cognitive dysfunction and dementia in the future. [8–13] The aetiology of delirium is multifactorial, with both modifiable and non-modifiable risk factors. [14,15] There is no known treatment for delirium, however a careful approach in the peri-operative period may reduce its incidence and severity. [6,9,15–18] Guideline committees have cautiously recommended that regional anaesthesia should be given unless contraindicated. [1,9,19] Despite this, the type of anaesthesia administered in patients with hip fractures remains varied. [4]

Ninety-eight percent of patients with hip fracture are offered surgery and will require anaesthesia. [5] Anaesthesia can be broadly classified into general (GA) or regional anaesthesia (RA). RA uses neuraxial blocks that avoid the use of GA drugs and opiates which have been linked to post-operative delirium. [3] Excessive depth of anaesthesia and perioperative hypotension have been reported in GA patients and are both
associated with an increased risk of mortality. [20] However, the risk of perioperative hypotension and sedation is not completely eradicated with RA. [21,22]

Findings from previous systematic reviews looking at the effects of type of anaesthesia on post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of out-dated anaesthetic drugs that are no longer relevant to current clinical practice. [5,24] Further limitations were the inclusion of only randomised controlled trials, [3,5,23,24] lack of focus on delirium as a primary outcome, [3,5,22,24,26] a limited search strategy [22] and restrictive selection criteria (e.g. exclusion of studies with patients with cognitive impairment). [23,25,26] Inadequate exploration of heterogeneity relating to delirium assessment and rating scales and assessment time points was also common. This systematic review aims to provide an up-to-date, comprehensive and methodologically robust analysis to examine the effect of RA versus GA on post-operative delirium and other outcomes in older patients undergoing surgery for hip fracture.

METHODS

The protocol for this systematic review has been published and is registered with PROSPERO (CRD42015020166). [27] A summary of the methods is outlined below. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [28]

Search strategy and selection criteria

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to June 2018 using a combination of index terms and key words relating to the population, intervention and comparator (see Appendix A for sample search strategy). There was no restriction by search date, study design or language. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial
registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

**Study selection**

Studies were eligible for inclusion if they met the following pre-defined criteria:

1) Population - patients aged ≥60 years (or with a majority ≥60) undergoing surgery for fragility hip fracture.
2) Intervention and comparator – one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK [19]
3) Outcomes – primary outcome: post-operative delirium (any criteria as defined by study authors); secondary outcomes: mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
4) Randomised or non-randomised controlled studies (prospective or retrospective).

Exclusion criteria for the primary outcome of ‘post-operative delirium’ were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthetic agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and uncontrolled studies. Two reviewers (RC, VP) independently screened titles and abstracts. Any disagreements were resolved with the support of JY. Reasons for exclusion were recorded at the full text stage.

**Data Extraction and Quality Assessment**

A piloted, standardised data extraction form was used to record information on study design, patient characteristics, type of surgery, anaesthesia type, and outcomes. The Cochrane Collaboration risk of bias tool [29] was used to assess the methodological quality of randomised controlled trials and the Newcastle-Ottawa scale [30] for non-randomised studies. Full translations could not be obtained for three included studies.
extracted data is therefore based mainly on numerical data and the English abstract. Data was extracted by RC and VP, with data checking by JY (for RC) and JD (for VP).

Data analysis and synthesis

Findings were grouped according to outcome. Where there was sufficient data, results were presented in forest plots (delirium, mortality and length of hospital stay). Effect estimates were not pooled as clinical and methodological heterogeneity was considered to be too great. Forest plots were thus used for illustrative purposes only and potential sources of heterogeneity (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. results reported narratively only, or a p-value only stated) results or conclusions from the study were nonetheless described in order to report the totality of the available evidence. Occurrence of delirium and mortality were reported as relative risks or odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative morbidity survey (POMS) criteria. [34] Findings for other outcomes (functional outcomes, quality of life, and discharge location) were reported narratively as heterogeneity and/or a paucity of data precluded representation in forest plots. Formal sensitivity analysis according to study quality, and assessment of publication bias using funnel plots were not possible.

Patient and Public Involvement

This systematic review is part of a programme of research looking at impact of anaesthesia on post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS Foundation Trust.

RESULTS
Of 4859 citations screened, 104 studies met the eligibility criteria (Figure 1). There were 7 randomised controlled trials (RCTs), 34 prospective and 63 retrospective controlled studies.

Twenty-two studies reported delirium (5 RCTs, [35–39] 9 prospective [18,40–47] and 8 retrospective studies [48–55]; 58 studies reported mortality (2 RCTs, [35,38] 12 prospective [42,45,56–65] and 45 retrospective studies [4,20,21,31,32,48,51,52,54,66–100]); 25 studies reported length of hospital stay (2 RCTs, [36,38] 6 prospective, [42,45,58,101–103] and 17 retrospective studies [21,51,57,68,70,71,75,78,80–83,95,104,105,98,99]); 27 studies reported adverse events (4 RCTs [35,36,39,106] 7 prospective [42,43,45,58,101,107,108] and 16 retrospective studies [20,21,48,51,52,68,69,71,75,79–81,95,96,109,110]); 11 studies reported functional outcome (3 RCTs, [35,36,111] 4 prospective [42,45,103,112] and 4 retrospective studies [62,73,105,113]) and 5 studies reported discharge location (2 prospective [43,114] and 3 retrospective studies [21,48,99]).

Thirteen potentially relevant ongoing trials were identified, with three (ISRCTN15165914, NCT03318133 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics

Given the large number of studies identified, only the 22 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium

Fifteen studies reporting unadjusted results are represented in the forest plot (Figure 2), including four of the five RCTs. One RCT[Neuman] was a small pilot study with 12 patients. Based on these 15 studies, only one study found a statistically significant benefit in favour of regional anaesthesia [49] and overall there is no evidence of a benefit of one type of anaesthesia over another. Five further studies not represented in...
the forest plot (one RCT, [35] two retrospective analyses reported as abstracts only, [50,53] and one prospective study [31]) also found no significant differences in delirium based, where stated, on Abbreviated Mental Test (AMT) or DSM-IV (one RCT, [35] two retrospective analyses reported as abstracts only, [50,53] and two prospective studies [31,46], one of which [46] was reported as an abstract).

One retrospective study [55] found a statistically significant difference in immediate (within 24 hours) delirium with GA for both adjusted and unadjusted results (based on CAM); there was no difference for delayed delirium. A further study [47] also found that delirium was more common with GA, but this did not remain statistically significant on multivariate analysis. The assessment tool for delirium was not stated. Four other studies [42,52,53,115] also presented adjusted results, two of which are also represented in the above plot [42,52](Figure 2). None found that type of anaesthesia was predictive of post-operative delirium.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the assessment tools used [38] and method of randomisation. [35,36,38,39] Blinding of outcome assessment was either not undertaken [38] or unclear, [36] although two RCTs had a clear statement on blinding. [35,39] There appeared to be no loss to follow-up in three RCTs [36,38,39], but this was unclear for the other RCT. [35] The RCT by Kamitani was not quality assessed as a full translation was not available. [37]

The observational studies were generally considered to be at low risk of bias in terms of patient eligibility, however most had no details on blinding of outcome assessors and the level of completeness of data was not well described (Table 2b). There was variation in terms of which confounders were adjusted for. Five studies reported details; all included ASA score as well as a range of factors including age, gender, co-morbidities, surgery type, time to surgery and physical functioning. There were no details on characteristics of completers compared with those lost to follow up. There was also a lack of detail on the type of assessment tool used and/or where the cut-off for a “positive” diagnosis of delirium was. This lack of detail is likely to be due in part to the fact that several studies were reported in abstract form only.
Most studies did not adjust for potential confounders, but four studies [31,42,52,53], one of which is also represented in the above plot [52], did present adjusted results. There was some variation in terms of which confounders were adjusted for (see Table 2b for details). Three studies reported these in full; all included age, gender and ASA score as well as a range of factors including co-morbidities, surgery type and physical functioning. None found that type of anaesthesia was predictive of post-operative delirium.

There was substantial heterogeneity across the 22 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 7 out of 22 studies used either DSM-IV criteria [18,31,49,53,54] or AMT. [35,50] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

Secondary outcomes

Mortality

Two RCTs reported mortality (Table 3). One found a small and statistically significant survival benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Ten observational studies reported adjusted results or results based on a matched analysis (Table 3). Two of these [20,68] found a statistically significant benefit in favour of RA for in-hospital mortality. The remaining eight studies found no significant differences. There was a lack of consistency across studies in terms of number and type of variables included in models.

Of the remaining 46 studies (results not shown) reporting unadjusted mortality results only, six [56,60,67,73,74,76] found statistically significant results in favour of RA. The remainder found no statistically significant differences and no consistent trend of benefit.
Overall there is a paucity of good quality evidence evaluating mortality, with only one good quality RCT [38] suggesting benefit from GA at later, but not earlier time points.

Length of hospital stay

Twenty-five [21,36,38,42,45,51,57,58,68,70,71,75,78,80–83,95,101–105,98,99] studies reported length of hospital stay; nine could be included in a forest plot (Figure 3). There was no difference in length of hospital stay based on one RCT. [38] The matched/adjusted results, based on three retrospective studies, [21,68,81] showed a slight trend towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,68] the absolute reduction was small (up to around a third of a day). Results from the studies reporting unadjusted results were inconsistent, with three finding no difference, [71,75,80] and two finding a benefit from RA. [82,101]

Of the remaining sixteen studies [36,42,45,51,57,58,70,78,83,95,102–105,98,99], neither the RCT [36] nor the five prospective studies [42,45,58,102,103] showed any significant differences. Results from the ten retrospective studies were also inconsistent (three studies [57,70,83] reported no difference, four studies [51,78,104,99] found a statistically significant benefit for RA [78] (only for proportion staying up to 6 days [104]) and one [95] a statistically significant benefit for GA.) Fukuda et al reported a statistically significant effect in favour of spinal anaesthesia, but this effect was lost after propensity score matching. [105] One large study (Nishi, n=16,687) reported in abstract form only reported a slightly shorter LOS with RA; it was unclear if this was statistically significant.[98]

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of twelve studies [21,36,45,51,57,70,71,83,95,102,103,99] reporting the median, nine studies [21,36,45,57,70,71,83,102,103] found no statistically significant differences. Three studies found a statistically significant difference in medians favouring RA [51,99] or GA [95] respectively.

Adverse Events
Twenty-seven studies reported adverse events (Table 4). There were many gaps in reporting of POMS adverse events, and it is uncertain whether this reflects non-occurrence or non-reporting of such events. Most commonly reported adverse events were pulmonary (10 studies) [20,21,35,45,48,49,62,69,89,91] and cardiovascular events (9 studies). [21,35,39,48,58,68,69,81,95] For pulmonary events, six studies found no statistically significant differences. [35,45,49,69,89,91] Four studies found a statistically significant difference in favour of RA (fewer cases of ventilatory support [68], respiratory failure [20,68] and ‘overall pulmonary’ adverse events [20,51]). There were no differences in occurrences of pneumonia [35,48,52,95] or hypoxia. [75,101] The most commonly reported cardiovascular adverse events were myocardial infarction [39,48,68,95] and thromboembolic events. [35,58,69,81,95] No differences were found for myocardial infarction. [39,48,52,68,75,95] Three studies [69,81,95] reported higher incidence of thromboembolic events in GA group.

Nine studies summarised overall adverse events with the majority finding no differences between the types of anaesthesia. Where there was a significant difference, this was in favour in RA (e.g. fewer incidences of ‘all complications’, [51,69] ITU admissions, [68] stroke [68] or requirement for blood transfusion). Three studies [106,108,109] found higher incidences of hypotension in the GA group.

The results are thus suggestive of a lower incidence of post-operative respiratory, cardiac and overall complications in the RA group. However, reporting of adverse events, including methods of ascertainment, was inconsistent and limited.

Functional outcomes

Eleven studies reported functional outcomes using a variety of outcome measures. Two RCTs reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] and a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in the RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005) [36]. However one RCT found that patients given RA was slower to be discharged from PACU (Mean time to discharge GA 35.04min (SD 3.39) vs RA 41.26min (SD 8.37), p=0.001).[111] No significant differences were found in the non-randomised
studies regarding time to ambulation, [103,112,113] walking speed, [62] time to rise from chair, [42] mean Barthel's score [73] or ambulation at 3, 6 and 12 month postsurgery. [45,105] Overall results may suggest a small benefit from RA for immediate post-anaesthetic mobilisation. However, the evidence is limited by small sample size, unknown method of outcome assessment and blinding of assessors.

**Discharge location**

Five non-randomised studies described discharge locations of patients following hip fracture. [21,43,48,99,114] One study with only 14 patients reported that more patients returned home in the RA group [45]. A large retrospective study reported lower odds of returning to home residence and higher chance of admitting to healthcare facility in GA group compared to RA (16695 patients, return home adjusted OR 0.91 (95%CI 0.84, 0.97); healthcare facility admission OR 1.10 (95%CI 1.03, 1.19). [99] A cohort study of 4815 patients found operation under GA significantly increased risks of rehabilitation admission instead of home (adjusted OR 1.74, 95%CI 1.34, 2.25, p<0.001). [114] However, two larger studies [21,109] found no difference in discharge location between GA or RA groups.

**Quality of Life**

There were no studies that evaluated the effect of type of anaesthesia on quality of life in patients after hip fracture surgery.

**DISCUSSION**

For the primary outcome of post-operative delirium, this systematic review did not find any difference between types of anaesthesia. Furthermore, no survival benefit could be demonstrated with either type of anaesthesia up to one year post-operatively. A small number of studies suggested that fewer adverse events might be associated with RA. Similarly some studies were suggestive of a small reduction in hospital stay with RA. Data was limited for functional outcomes and discharge data. Two small RCTs suggested
a benefit from RA for immediate post-anaesthetic mobilization. There were no studies that reported on quality of life after different types of anaesthesia.

This is the most comprehensive and methodologically robust systematic review to date. It includes both RCTs and non-randomised controlled studies, focusing on delirium as a primary outcome as well as synthesising findings for a range of other important outcomes including adverse events. Results for RCTs, non-randomised studies, adjusted and unadjusted results were presented and considered separately. It was anticipated that non-randomised studies, which are more prone to bias, may overestimate effect sizes compared with RCTs. No such trends were observed however, as studies of any design mostly showed no difference in effect.

A sensitive search strategy means it is unlikely that many studies would have been missed. Careful consideration of heterogeneity has meant that no meta-analyses were undertaken, but results were presented in forest plots where possible to show the overall direction of effect and heterogeneity between studies.

Delirium can be diagnosed using the criteria from the DSM-V or the WHO’s ICD-10 classification of diseases. [7,116] However in clinical practice the criteria can be difficult to apply [117] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [118] or 4AT have been advocated as validated screening tools. (4 ‘A’s’ Test) [6,117,119] No consensus exists in the literature as to which tool should be the gold standard. [6,120,121] The accurate assessment of delirium can be affected by the presence of pain and residual drugs in the immediate period following surgery therefore timing of assessment is also important. [122] No significant differences were found for the incidence of post-operative delirium, based on four RCTs and 14 non-randomised studies but there were significant differences in the assessment tools and the assessment time-points. Most of the RCTs were small and most likely underpowered. In the largest RCT [38] delirium was not a primary outcome and the assessment tool used or the timing of assessments was not reported. The pathophysiology of delirium remains poorly understood but there are a combination of pre-existing and precipitating factors that can pre-dispose the patient to post-operative
delirium. [11,123,124] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [125,126] are associated with higher risk of delirium. Precipitating factors can include acute injury such as a hip fracture, malnutrition, electrolyte imbalance and the use of urinary catheter and physical restraints. [126] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain. [127,128] The studies that adjusted for confounders and reported delirium [31,42,52,53] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. [42,52,53] However, with multifactorial risk factors for delirium, it is difficult to encompass all variables. Other important characteristics such as anaemia, time to surgery, blood loss, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in terms of number and type of variables included in models and the reporting of these, it is not possible to gauge the overall impact that adjusting for confounders may have on the direction of effect.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total number of patients included for the primary outcome) and many of the non-randomised studies did not make any attempts to adjust for potential confounding factors. When confounding variables were considered, this was often done for mortality only. There was significant heterogeneity across studies in study design, population age, comparators, assessment time-points and definition of outcomes (particularly delirium) that precluded quantitative pooling.

Detailed reporting of anaesthetic techniques was suboptimal especially for GA techniques. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium [3,129] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst most studies planned to collect adverse events data, it was unclear whether adverse events were predetermined. Small sample sizes (n<30) and rare occurrences of adverse events means that many studies were likely underpowered. [35,36,48,101].
The style of data reporting in included studies could also lead to over-reporting of complications; for example, a patient could develop pneumonia, which led to respiratory failure and the need for inotropic and ventilatory support and ITU admission. Thus five adverse events would be attributable to a single patient, but this may not be evident from the data. Incidence of intraoperative hypotension was not captured by POM categories, as inotropic support use was not reported. Hypotension can lead to hypoperfusion and organ damage. A recent analysis of data from an audit of outcomes in hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [106,108,109] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [52,69,106,109] also found significantly higher volumes of fluids and blood products transfused in the GA group.

Subgroup analysis was not feasible and no individual studies reported findings for different sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to GA that have not been captured by the evidence presented in this systematic review. Subgroup analysis of specific at risk patients, for example the frail and the very elderly, may suggest a benefit for either regional or general anaesthesia in certain population groups.

Older patients are at high risk of adverse outcomes post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [130] Principles of care for older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [131] Most recently, the European Society of Anaesthetiology consensus-guideline on post-operative delirium also did not find substantial evidence to recommend a specific type of anaesthetic technique but advocates intraoperative monitoring to avoid swings in blood pressure and excessive depth of anaesthesia. [132] Given the lack of standardised assessment tools of delirium and the paucity of suitably powered, methodologically sound studies, uncertainty remains regarding any potential benefits of certain types of anaesthesia. However, even a modest reduction in adverse events and length of hospital stay could benefit many patients and result in cost savings for health care providers.
Future research examining post-operative delirium should include robust assessment and diagnosis of delirium. There is also an urgent need for high quality research comparing anaesthetic techniques that focus on patient-related outcomes such as quality of life and functional outcomes.
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Author Contributions
All authors have made substantial contributions to the manuscript. JY: the conception and design of the study, VP/RC/JD/JY acquisition of data, analysis and interpretation of data, VP/RC/JD/JY drafting the article or revising it critically for important intellectual content, VP/RC/JD/JY final approval of the version to be submitted. We would like to thank Mrs Preeti Pulgari for her assistance with the review.

Data sharing statement
There are no unpublished data from this review.
Table 1: Table of characteristics of studies that measured postoperative delirium

| Author       | Year | Country     | ASA                     | Comparison and number of patients | Population                                 | Age, mean age and M/F split | Outcomes measured                  |
|--------------|------|-------------|-------------------------|----------------------------------|--------------------------------------------|------------------------------|------------------------------------|
| Bigler       | 1985 | DENMARK     | General: ASA 1: 2 ASA 2: 14 ASA 3: 4 Spinal: ASA 1: 2 ASA 2: 15 ASA 3: 3 | General (n=20) v Spinal (n=20) | Patients having acute surgery for hip fracture | Patients above 60 years of age Mean age General: 77.6 years (SEM 2.3) Spinal: 80.1 years (SEM 1.6) M/F: 7/33 | -Postoperative mental function -Morbidity |
| Casati       | 2003 | ITALY       | General: ASA 2: 7 ASA 3: 8 Spinal: ASA 2: 6 ASA 3: 9 | General (n=15) v Spinal (n=15) | Patients undergoing hip fracture repair | Patients over 65 years of age Mean age General: 84 years (range 67-88) Spinal: 84 years (range 71-94) M/F: 2/28 | -Hypotension -Cognitive dysfunction |
| Kamitani     | 2003 | JAPAN       | ASA not reported. Comparable 'physical status' between GA and RA groups | General (n=21) v Spinal (n=19) | Patients with femoral neck fracture | Patients aged 70 and over Mean age General: 81.4 (SD 6.2) Spinal: 83. (SD 6.0) M/F: 4/36 | -Postoperative delirium |
| Neuman       | 2016 |             | No details              | General (n=6) v spinal (n=6) | Femoral neck or pertrochanteric hip fracture surgery | Patients aged 18 and over Median age (GA): 62.5 (57-88) | Primary: -Postoperative delirium |
| Country | Study Type | Authors | Study Design | Sample Size | Age | Gender | Primary Outcomes | Secondary Outcomes |
|---------|------------|---------|--------------|-------------|-----|--------|----------------|-------------------|
| USA | Feasibility study/Letter | Parker & Griffiths 2015 UK | General: ASA Grade 1 or 2: 98 Spinal: ASA Grade 1 or 2: 94.9 | Patients with acute hip fracture | Median age (RA): 80.5 (62-92) M/F: 9/3 | Secondary: Mortality |
| | | | General (n=164) v Spinal (n=158) | Patients over 49 years of age Mean age General: 83.0 years (range 59-99) Spinal: 82.9 years (range 52-105) M/F: 87/235 | Primary: Mortality Secondary: Surgical outcomes General complications Hospital stay |
| | PROSPECTIVE STUDIES | Atay 2012 TURKEY | Unable to obtain full translation. | General (n=30) v Spinal (n=40) | Patients with hip fractures | Patients aged 60 years and over Mean age M/F | Postoperative delirium Postoperative cognitive function |
| | | Bitsch 2006 DENMARK | ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10 | General (n=13) v Regional (n=83) | Hip fracture patients | No age restriction Mean age No significant decline: 81.6 years (range 75-86) Significant decline: 84.5 years (range 81-89) M/F: 28/68 | Risk factors for pre, intra and postoperative cognitive dysfunction |
| | | Bjorkelund 2010 SWEDEN | Intervention group (new care plan): ASA 1=17 ASA 2=59 ASA 3=48 ASA 4=7 Control group | General (n=89) v Spinal (n=174) | Patients with hip fractures | Patients aged 65 years and over Mean age Intervention: 81.1 years (SD 7.5) Control: 82.0 years (SD 7.6) M/F: 78/185 | Incidence of Delirium |
| Study | Year | Location | General | Spinal | Patients with an acute hip fracture | Age | Complications (in-hospital and surgical) | Functioning (daily, social, mental) |
|-------|------|----------|---------|--------|-------------------------------------|-----|----------------------------------------|-----------------------------------|
| Gilbert | 2000 | USA      | General: ASA 1-2: 105 ASA 3-4: 194 | Spinal: ASA 1-2: 109 ASA 3-4: 309 | General (n=311) v Spinal (n=430) | Age 65 years and older | Age General: 65-79 years n=120 80+ years n=191 Spinal: 65-79 years n=184 80+ years n=246 M/F: 156/585 |
| Ilango | 2015 | AUSTRALIA | Not reported | General (n=167) v Spinal (n=151) | Hip fracture patients | Age not specified within inclusion criteria | Mean age General: 81.3 years (SD 10.5) Spinal: 82.1 years (SD 9.0) M/F: 89/229 |
| Juliebo | 2009 | NORWAY   | ASA 1 or 2 = 182 | General (n=20) v Spinal (n=337) | Patients with hip fracture | Patients aged 65 years and over | Age Delirium: 85 years (range 82-89) No delirium: 82 years (range 77-87) M/F: 88/276 |
| Koval   | 1999 |          | General: ASA 1 or 2: 236 | General (n=362) v Spinal (n=280) | Patients who sustained a hip fracture | Patients 65 years of age and older | Inpatient medical complication rate Hospital mortality rate |
| Country   | ASA 3 or 4: | Mean age | 1 year mortality rate |
|-----------|-------------|----------|-----------------------|
| USA       | 120         | General: 78.5 years, Spinal: 81.0 years, M/F: 129/513 | - |

| Study     | Numbers in GA, GA + block, spinal and spinal + block groups not stated | Total n=85 | Hip fracture patients | No details. | Delirium |
|-----------|------------------------------------------------------------------------|-----------|-----------------------|------------|----------|
| Mohamed   | No details                                                              | Hip fracture patients | No details. | Delirium |
| 2017 UK   | Total n=85                                                              | Hip fracture patients | No details. | Delirium |
| Ojeda     | Total n=303                                                              | Patients aged 70 years and over. | Mean age: 84 (SD 6), M/F: 39%/61% | Delirium |
| 2018 Spain| Numbers in GA and RA groups not stated.                                  | Patients undergoing hip fracture surgery | Patients aged 65 years and older | In-hospital complications |
| RETROSPECTIVE STUDIES | General v Spinal v Peripheral nerve block 392 included patients, but no breakdown of who received what anaesthesia | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
| Bellelli  | Not reported                                                            | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
| 2013 Italy| 392 included patients, but no breakdown of who received what anaesthesia | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
| Choi      | For those who developed delirium:                                     | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
| 2017 Korea| ASA 2: 10                                                             | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
|          | ASA 3: 97                                                              | Patients with femoral neck fracture | Patients aged 70 years and over | Immediate and delayed delirium |
| Study | Country | ASA 4: 3 | ASA 1: 6 | General (n=246) v Spinal (n=249) v Epidural (n=11) | Hip fracture surgery patients | Patients aged 60 years and over | -30 day postoperative complications |
|-------|---------|----------|----------|-------------------------------------------------|-----------------------------|-------------------------------|-----------------------------------|
| Kim   | KOREA   | ASA 2: 311 | ASA 3: 189 | Age 60-69 years n=83 70-79 years n=227 >80 years n=196 | M/F: 140/366 | | |
| Konttinen | FINLAND | ASA 3: 8 | ASA 4: 6 | General (n=3) v Spinal (n=11, single shot: 5, continuous: 6) (14 procedures in 12 patients) | Patients undergoing major emergency surgery | Patients aged 100 years and over | M/F: 2/10 |
| Luger  | AUSTRIA | Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2 Control: 2.8 +/- 0.6 | General (n=116) v Regional (n=213) | Patients scheduled for acute hip fracture surgery | Patients aged 80 years of age and older | M/F: 19/51 |
| Michael | UK | Abstract | Not reported | General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia) | Hip fracture patients | Patients aged 60-100 years | Pre and post-operative cognitive function |

- Cardiac complications
- Pulmonary complications
- Delirium
- Death
- Intraoperative variables
- Complications
- Post-op discharge location
- Pain management
- Haemodynamics
- Mental status
- Mobilisation
- Mortality
- Cognitive decline
- Time to surgery
- Length of hospital stay
- Pre and post nursing home stay
- Comorbidities
- Perioperative Complications

Mean ASA:
- Group 1 (post-op delirium): 2.9 +/- 0.6
- Group 2 (unspecified cognitive dysfunction): 88.4 +/- 5.2
- Control: 2.8 +/- 0.6

Age:
- Delirium: 87.9 years (SD 4.5, range 81-97)
- No delirium: 88.8 years (SD 5.3, range 81-100)

M/F: 19/51

-60-70 years n=50
-70-80 years n=169
-80-90 years n=338
-90-100 years n=147
| Study | Country | Study Population | Study Design | Sample Size | Age Groups | M/F | Outcomes |
|-------|---------|------------------|-------------|-------------|------------|-----|----------|
| O’Hara 2000 USA | General: ASA 1 or 2: 1698 ASA 3: 3666 ASA 4 or 5: 618 Regional: ASA 1 or 2: 560 ASA 3: 2097 ASA 4 or 5: 438 | Patients 60 years of age or older | General (n=6206) v Regional (n=3219, spinal n=3078 and epidural n=141) | M/F: 178/526 | 60-69 years n=910 70-79 years n=1918 80-89 years n=2602 90+ years n=776 | Regional: 60-69 years n=325 70-79 years n=881 80-89 years n=1452 90+ years n=561 | Primary: -30 day mortality Secondary: -7 day mortality Other: -7 day morbidity |
| Shih 2010 TAIWAN | General: ASA 2: 47 ASA 3: 115 ASA 4: 1 Spinal: ASA 2: 45 ASA 3: 120 ASA 4: 2 | Patients undergoing hip fracture repair | General (n=167) v Spinal (n=168) | M/F: 2010/7415 | Patients aged 80 and over Mean age General: 83.96 years (SD 3.71) Spinal: 84.93 years (SD 4.04) | M/F: 189/146 | -Postoperative morbidity -Postoperative mortality -Pre and intraoperative variables |

ASA is American Society of Anesthesiologists Physical Status Classification System; SD is standard deviation. SEM is standard error of the mean.
**Table 2a: Quality assessment of RCT studies reporting delirium**

AMT is Abbreviated mental test  
CAM is Confusion assessment method  
DRS is Delirium Rating Scale  
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition  
MMSE is Mini mental state examination

| Study          | Randomisation | Concealment of allocation | Similarity at baseline | Blinding of outcome assessor | Incomplete outcome data (for outcome of delirium) | Validity of assessment tool | Assessment tool specific for delirium | Selective reporting |
|----------------|---------------|---------------------------|------------------------|-----------------------------|-------------------------------------------------|-----------------------------|-------------------------------------|---------------------|
| Neuman 2016    | UNCLEAR       | UNCLEAR                   | Groups similar for age, gender and comorbidities. | LOW | Blinded research coordinators assessed outcomes. | LOW Results reported for all patients. | CAM good validity for identifying delirium | Yes | UNCLEAR |
| N=12 (Letter)  | No details.   |                           |                        |                             |                                                 |                             |                                     |                    |
| Parker & Griffiths 2015 | UNCLEAR | LOW | Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group). | HIGH | No blinding of outcome assessors | LOW | Unclear-no details | Unclear | UNCLEAR |
| N=322          | Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial. | | | | | | | |
| Casati 2003    | UNCLEAR       | LOW                       | Groups similar for all baseline characteristics measured | UNCEar | Clinical criteria for patient's discharge applied by staff blinded to anaesthetic technique-but no details for applying MMSE. | LOW | MMSE for all 30 patients at 1 and 7 days. | MMSE good validity for cognitive function | No | UNCLEAR |
| N=30           | "Using a sealed envelope technique, patients were randomly allocated..." | | | | | | | |
| Bigler 1985    | UNCLEAR       | UNCLEAR                   | Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group. | LOW | Surgeon undertaking AMT unaware of anaesthesia given | UNCEar | No details on proportion that AMT was undertaken in at 7 days and 3 months. | AMT good validity for cognitive dysfunction | No | UNCLEAR |
| N=40           | No details. (other than "patients randomly allocated") | No details | | | | | | |

**NB** Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.
Table 2b: Quality assessment of observational studies reporting delirium

| Study               | Eligibility criteria                                                                 | Confounders Low risk                                                                 | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data                                                                 |
|---------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------|-----------------------------------------------------------------------------------------------|
| Belleli 2013 (Abstract) | Patients aged > 65 years admitted to one orthogeriatric unit between 2007 and 2011.   | HIGH for unadjusted data LOW for adjusted data                                      | UNCLEAR                       | LOW                             | Yes                       | Patients with incomplete data in medical records were excluded from this study. Proportion not stated. |
| Bitsch 2006          | Consecutive patients but large number excluded and unclear if similar characteristics to included | HIGH                                                                                | UNCLEAR                       | LOW-good validity for cognitive function | No                        | HIGH                                                                                           |
| Björkelund 2010      | Consecutive patients included                                                        | HIGH                                                                                | UNCLEAR                       | LOW                             | No for DSM-IV              | No loss to follow-up from included patients for delirium assessment                            |
| Study      | Eligibility criteria | Confounders | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------|----------------------|-------------|-----------------------------|---------------------------------|---------------------------|-------------------------------|
| Choi 2017  | LOW                  | HIGH for unadjusted data | LOW                        | CAM, CAM-IUC                    | Yes                        | LOW                           |
|            |                      | LOW for adjusted data    |                             |                                 |                           |                               |
|            |                      | Variables adjusted for were age, previous dementia, parkinsonism, ASA grade and ICU care. | Assessment made by independent psychiatrist |  |  | 
| RETROSPECTIVE | Consecutive patients included | Unclear | No details | Unclear | Unclear | Appears to include all eligible consecutive patients. |
| Gilbert 2000 | LOW                  | HIGH for unadjusted data | Unclear | LOW (MMSE) | High ("mental confusion") | Unclear |UNCLEAR |
|            |                      | LOW for adjusted data    |                             |                                 |                           |                               |
| PROSPECTIVE | Patients given general and spinal were drawn from the same population | Unclear | No details | Mental confusion not further defined; MMSE |  | No details-only how many included in final analysis |
| Ilango 2015 | LOW                  | HIGH                   | Unclear | HIGH | Subjective method ("clinical judgement") and several scales; cut-off unclear. | Unclear |UNCLEAR |
|            |                      |                        |                             |                                 |                           |                               |
| Juliebo 2009 | LOW                  | HIGH                   | LOW                        | CAM                            | Yes                        | HIGH                           |
|            |                      |                        |                             |                                 |                           |                               |
|            | All eligible hip fracture patients September 2005 to December 2006. | Univariate analysis only for type of anaesthetic and outcome. No details on similarity of groups for this variable. Adjusted analyses not with type of | Staff performing assessments were not involved in the care of |  |  | No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part. | 127/364 (35%) included not assessed pre-operatively | 19/337 (6%) incomplete data. No details on characteristics. |
| Study            | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------------|----------------------|----------------------|-------------------------------|---------------------------------|---------------------------|--------------------------------|
| Kim 2013         | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | Yes                       | LOW (anaesthetic as a variable.) and excluded. No details on their characteristics. |
| Kontinnen 2006   | LOW                  | HIGH                 | UNCLEAR                       | UNCLEAR                         | Unclear                   | UNCLEAR (no details on similarity of baseline characteristics for groups). |
| Koval 1999       | LOW                  | HIGH                 | UNCLEAR                       | UNCLEAR                         | Unclear                   | UNCLEAR (no details on baseline characteristics for groups). |
| Luger 2014       | LOW                  | HIGH                 | UNCLEAR                       | LOW (DSM-IV)                    | Yes (DSM-IV)              | HIGH (82/411 (20%) excluded due to incomplete records. Unclear if excluded had different characteristics to those included) |
| Michael 2014     | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | Yes                       | UNCLEAR (34/738 (5%) excluded retrospectively. No reasons for exclusions). |
| Mohamed 2016     | UNCLEAR              | HIGH                 | UNCLEAR                       | UNCLEAR                         | Unclear                   | LOW (4.4% of patients lost to follow-up. No further details). |
| Study       | Eligibility criteria                                                                 | Confounders Low risk                                                                 | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------|------------------------------|
| (Abstract) | Patients from 6 hospitals; no further details                                        | No details on baseline characteristics between groups. No adjusted analyses.        | No details.                   | No details.                     | Data from enrolled patients analysed. |
| O'Hara 2000| **LOW**                                                                               | **HIGH** for unadjusted data; **LOW** for adjusted data                              | **UNCLEAR**                   | **UNCLEAR**                     | Unclear                   | **UNCLEAR**                  |
| RETROSPECTIVE | Consecutive patients from 20 hospitals                                                | Appear to be some baseline imbalances between groups, but multivariate analyses.   | No details                    | Not clearly defined             | 9425/9598 < 2% missing       |
| Ojeda 2018 | **UNCLEAR**                                                                          | **HIGH** for unadjusted data; **LOW** for adjusted data                              | **UNCLEAR**                   | **UNCLEAR**                     | Unclear                   | **UNCLEAR**                  |
| (Abstract) | Patients over 70 years admitted with a hip fracture; no further details.              | Unclear if any baseline imbalances. Variables in multivariate analysis were time to surgery, ASA status and comorbidities. | No details.                   | No details.                     | No details.                |
| Shih 2010  | **LOW**                                                                               | **HIGH**                                                                            | **UNCLEAR**                   | **UNCLEAR**                     | Unclear                   | **LOW**                     |
| RETROSPECTIVE | Octogenarian patients undergoing hip fracture repair in one centre between 2002 and 2006. | Some baseline imbalances between groups; no adjusted analyses for delirium (only for “morbidity”) generally. | No details                    | Not clearly defined             | Appears to be no missing data from those patients included. |

NB Quality assessment was not performed for Atay [31] as a full translation was not available.
Table 3  Mortality results

| Study               | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI) | Adjusted/matched OR or RR (95% CI) | Note                                                      |
|---------------------|------------|---------------------|---------------------|-----------------------------|-----------------------------------|-----------------------------------|
| RCTs                |            |                     |                     |                             |                                   |                                   |
| Bigler 1985         | In-hospital| 1/19                | 1/19                | RR=1.00 (0.07, 14.6)        |                                   | No statistically significant difference in in-hospital mortality. |
| Parker & Griffiths 2015 | 30 day     | 8/156               | 5/153               | RR=1.54 (0.52, 4.58)        |                                   | No statistically significant difference in mortality at 30 or 90 days. |
| Parker & Griffiths 2015 | 90 day     | 12/152              | 12/146              | RR=0.96 (0.45, 2.07)        |                                   | Statistically significant difference in mortality at 120 days and 1 year in favour of GA. |
| Parker & Griffiths 2015 | 120 day    | 12/152              | 15/143              | RR=0.77 (0.61, 0.91)        |                                   |                                   |
| Parker & Griffiths 2015 | 1 year     | 19/145              | 32/126              | RR=0.57 (0.34, 0.96)        |                                   |                                   |
| Prospective cohort  |            |                     |                     |                             |                                   |                                   |
| Withey 1995         | 1 year     | Total only reported: 303 | Total only reported: 161 | Not reported. | OR 1.28 (0.76, 2.14) | No statistically significant difference in mortality (adjusted data). |
| Zhao 2015           | Unknown    | 65/166              | 22/238              | Not reported. | OR 0.687 (0.248, 1.906) | No statistically significant difference in mortality (adjusted data). |
| Retrospective cohort |            |                     |                     |                             |                                   |                                   |
| Chu 2015            | In-hospital| 1363/ 50681         | 1107/ 50937         | Not reported. | OR 1.24 (1.15, 1.35) | Statistically significant difference in mortality (adjusted data) in favour of RA. |
| Neuman 2012         | In-hospital| 325/12579           | 110/5144            | Not reported. | OR 0.710 (0.541, 0.932) | Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA). |
| Paterno 2014        | In-hospital| 1477/66345          | 144/6939            | RR 0.94 (0.79 to 1.11)     | RR 0.93 (0.78 to 1.11)           | No statistically significant difference in mortality (adjusted or unadjusted). |
| O’Hara 2000         | 7 day      | 82/6124             | 53/3076             | OR 0.80 (0.56-1.13)         | OR 0.90 (0.59-1.39)              | No statistically significant difference in mortality (adjusted or unadjusted). |
| Basques 2015        | 30 day     | 450/6803            | 166/2423            | 0.97 (0.81 to 1.17)         | OR 0.98 (0.82 to 1.20)           | No statistically significant difference in mortality (adjusted or unadjusted). |
| O’Hara 2000         | 30 day     | 272/5934            | 174/2955            | OR 0.80 (0.66-0.97)         | OR 1.08 (0.84-1.38)              | No statistically significant difference in mortality (adjusted or unadjusted). |
| Qiu 2018            | In hospital| 226/9629            | 111/6597            | Not reported               | HR 1.38 (1.10-1.73)              | No statistically significant difference in mortality |
| Seitz 2014          | 30 day     | 1044/7774           | 1450/10705          | RR 0.99 (0.92, 1.04)        | RR 1.04 (0.94, 1.15)             | No statistically significant difference in 30 day mortality |

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| Study          | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI)                   | Adjusted/matched OR or RR (95% CI)            | Note                                                                 |
|---------------|------------|---------------------|---------------------|------------------------------------------------|---------------------------------------------|------------------------------------------------|
| Whiting 2015  | 30 day     | Total only stated: 5840 | Total only stated: 1924 | OR 1.07 (calculated based on raw data reported) | (calculated based on raw data reported)     | (matched or unmatched). |

Spinal and regional nerve blocks
- OR 1.18 (0.91, 1.53)
- Spinal only
  - OR 1.20 (0.92–1.56)
- Regional only
  - OR 1.22 (0.54–2.76)

No statistically significant difference in 30 day mortality (adjusted data).

OR is odds ratio; RR is relative risk
Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio
GA vs. RA; NR = not reported; NS = not significant

| POMS categories | Study            | Adverse event description | GA          | RA          | Summary statistic*/p-value |
|-----------------|------------------|---------------------------|-------------|-------------|---------------------------|
| Pulmonary       | Basques 2015     | Ventilatory support       | 58/7253 (0.8%) | 13/2589 (0.5%) | NR                        |
|                 |                  | Pneumonia                 | 261/7253 (3.6%) | 108/2589 (4.2%) | NR                        |
|                 | Bigler 1985      | Pneumonia                 | 2/20         | 1/20        | NR                        |
|                 | Chu 2015         | Respiratory Failure       | 868/5204 3 1.61% | 328/5204 4 (0.63%) | OR 2.71 (95%CI 2.38 to 3.01), p<0.001, Favours RA |
|                 |                  | Ventilatory support       | 4008/520 43 (7.70%) | 338/5204 4 (1.44%) | OR 6.08 (95%CI 5.59 to 6.61), p<0.001, Favours RA |
|                 | Konttinen 2006   | Pneumonia                 | 0/3          | 2/11        | NR                        |
|                 | Le Liu 2014      | Overall pulmonary         | 18/172 (25%) | 27/145 (25.5%) | P=0.934 NS                |
|                 |                  | Hypoxia                   | 19/72 (26.4%) | 23/145 (15.9%) | P=0.065 NS                |
|                 | Le Wendling 2012 | Overall pulmonary         | 17/235 (6%)  | 1/73 (1%)   | OR 2.2 (95%CI 0.7 to 7.2) P=0.0841, Favours RA |
|                 | Naja 2000        | Hypoxia                   | 2/30 (6%)    | 0/30 (0%)   | NR                        |
|                 | Neuman 2012      | Overall pulmonary         | 1030/129 04 (8.1%) | 359/5254 (6.8%) | P=0.005, Favours RA     |
|                 |                  | Respiratory Failure       | 1040/129 04 (5%) | 178/5254 (3.4%) | P<0.0001, Favours RA  |
| Study            | Category                      | Condition                              | Event Count | Event Rate (%) | Odds Ratio (95% CI) | p-value | Statistic Significance |
|------------------|-------------------------------|----------------------------------------|-------------|----------------|---------------------|---------|------------------------|
| O'Hara 2000      | Pneumonia                     | 174/6206 (2.8%)                        | 84/3219     | 2.6%           | OR 1.21 (0.87 to 1.68) | NS      |                        |
| Shih 2010        | Overall pulmonary             | 11/167 (6.6%)                          | 3/168       | 1.8%           | P<0.03              |         | Favours RA             |
| Basques 2015     | Myocardial infarction         | 137/7253 (1.9%)                        | 49/2859     | 1.7%           | NR                  |         |                        |
|                  | Thromboembolic                | 138/7253 (1.9%)                        | 25/2589     | 1.0%           | NR                  |         |                        |
| Bigler 1985      | Cardiovascular decompensation | 1/20                                   | 1/20        | NR             |         |                        |
| Chu 2015         | Myocardial infarction         | 188/5204 (3.6%)                        | 169/5204    | 0.32%          | OR 1.11 (0.9 to 1.37), p=0.31 | NS      |                        |
| Fields 2015      | Thromboembolism               | 1.64%                                  | 0.72%       | P=0.004        | Favours RA         |         |                        |
| Konttinen 2006   | Myocardial infarction         | 0/3                                    | 1/11        | NR             |         |                        |
| Neuman 2016      | Myocardial infarction         | 1/6                                    | 0/6         | NR             |         |                        |
| Le Wendling 2012 | All cardiovascular complications | NR                                    | NR          | OR 1.7 (0.4 to 6.3) | NS      |                        |
| Seitz 2014       | Deep vein thrombosis          | 47/8818 (0.5%)                         | 41/12155    | 0.3%           | P=0.03              | NS when matched |                        |
|                  | Pulmonary Embolism            | 100/8818 (1.1%)                        | 93/12155    | 0.8%           | P=0.006             | NS when matched |                        |
| Sutcliffe 1994   | Deep vein thrombosis          | 16/950 (1.7%)                          | 14/383      | 3.7%           | P<0.05 NS           |         |                        |
|                  | Pulmonary Embolism            | NR                                     | NR          | NS             |         |                        |
| Bigler 1985      | Wound infection               | 1/20                                   | 0/20        | NR             |         |                        |
| Study                  | Condition                        | Events | Controls | OR (CI)               | Significance   |
|-----------------------|----------------------------------|--------|----------|-----------------------|----------------|
| Fields 2015           | Urinary Tract Infection          | 5.76%  | 8.87%    | P<0.0001              | Favours GA    |
| Rashid 2013           | Urinary Tract Infection          | NR     | NR       | NS                    |                |
| Basques 2015          | Wound Infection                  | 94/7253 (1.3%) | 39/2589 (1.5%) | NS                   |                |
| Renal                 | Basques 2015                     | Acute Renal Failure | 29/7253 (0.4%) | 10/2589 (0.4%) | NS            |                |
| Bigler 1985           | Urinary retention                | 4/20   | 5/20     | NS                    |                |
| Chu 2015              | Acute Renal Failure              | 78/52043 (0.15%) | 56/52044 (0.11%) | P=0.06 NS          |                |
| Naja 2000             | Acute Renal Failure              | 2/30 (6%) | 0/30 (0%) | NS                    |                |
| Overall complications | Gilbert 2000                     | Serious medical complications | 55/311 (17.7%) | 79/430 (18.4%) | OR 0.92 (95%CI 0.61 to 1.4) NS |
|                       | Gilbert 2000                     | Fewer medical complications | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95%CI 0.90 to 1.82) NS |
|                       | Whiting 2015                     | Surgical complications | 15/311 (4.8%) | 19/430 (4.4%) | OR 1.08 (95%CI 0.65 to 1.21) NS |
|                       |                                   | Major complications | NR | NR | OR 1.43 (95%CI 1.16-1.77) NS |
|                       | Whiting 2015                     | Minor complications | NR | NR | OR 1.02 (95%CI 0.82 to 1.26) NS |
|                       | Fields 2015                      | All complications | NR | NR | OR 1.24 (95%CI 1.05 to 1.48) NS |
|                       |                                   | All complications | 2357/4813 (48.97%) | 830/1815 (45.75%) | OR 1.29 (95%CI 1.13 to 1.47), p=0.0002 Favours RA |
| Hekimoglu Sahin 2012  | All complications                | NR     | NR       | NS                    |                |
| Ilango 2015           | All complications                | NR     | NR       | NS                    |                |
| Koval 1999            | All complications                | 41/362 (11.3%) | 32/280 (11.4%) | NS                    |                |
| Study             | Complication Type         | Outcome | Matched Outcome | P-Value | Odds Ratio (95%CI)  |
|-------------------|---------------------------|---------|-----------------|---------|---------------------|
| Le Liu 2014       | All complications         | 17/72 (23.6%) | 50/145 (34.5%) | P=0.165 NS |
| Le Wendling 2012  | All complications         | NR      | NR              | OR 1.7 (95%CI 0.7 to 4.1) NS |
| Radcliffe 2013    | All complications         | 22%     | 19%             | Log regression model p=0.002 Favours RA |
| Shih 2010         | All complications         | 21/167 (12.6%) | 9/168 (5.4%) | P<0.02 Favours RA |
| Chu 2015          | ITU admissions            | 5743/520 (11.03%) | 3205/520 (6.16%) | OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA |
| Chu 2015          | ITU stay >3 days          | 1206/520 (2.32%) | 411/520 (0.79%) | P<0.001 Favours RA |
| Baumgarten 2012   | Pressure ulcers           | 10/328 (3.0%) | 18/313 (5.8%) | OR 1.3 (1.0-1.6) Favours GA |
| Casati 2003       | Hypotension requiring crystalloid infusion | 12/15 (80%) | 7/15 (46%) | P=0.05 NS |
| Maia 2014         | Intraoperative hypotension | 25/50 | 80/173 | P=0.014 Favours RA |
| Minville 2008     | Intraoperative hypotension | 35/42 (83%) | 74/109 (68%) | NS |
| Gadsden 2016      | Intraoperative hypotension | 569/745 | 1144/1528 | Favours RA P<0.0001 |
| Messina 2013      | Haemodynamic changes first 10min | Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA | Favours RA |
| Basques           | Blood transfusion         | 2843/725 | 851/2589 | Matched OR 1.34 (1.22 to 1.49), |
| Year      | Event         | Value 1 | Value 2 | p-value       | Conclusion            |
|----------|---------------|---------|---------|---------------|-----------------------|
| 2015     | Blood transfusion | 3 (39.2%) | (32.9%) | p<0.001       | Favours RA            |
| Fields 2015 | Blood transfusion | 45.49% | 39.34% | P<0.0001      | Favours RA            |
| Minville 2008 | Blood transfusion | 23% | 4% | P<0.05        | Favours RA            |
| Shih 2010  | Blood loss     | Median 250 (0-1600) ml | Median 200 (0-1200) ml | P=0.01        | Favours RA            |
| Chu 2015   | Stroke         | 840/5204 3 (1.61%) | 717/5204 4 (1.38%) | OR 1.18 (95%CI 1.07 to 1.31), p=0.001 | Favours RA |
| Le Liu 2014 | Stroke         | 5/72 (5.9%) | 4/145 (2.8%) | P=0.145 NS    |                       |

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported
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Figure Legends

**Figure 1:** PRISMA Flow Diagram. Legend: The PRISMA diagram details our search and selection process applied during the review.

**Figure 2:** Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR= relative risk, CI= confidence interval, MMSE= mini mental state examination, CAM= confusion assessment method, DSM-IV= Diagnostic and statistical manual of mental disorders 5, UCD= unspecified cognitive dysfunction.

**Figure 3:** Forest plot of studies reporting length of hospital stay. WMD= weighted mean difference, CI= confidence interval
| Study                | Assessment tool | Time-point          | RR (95% CI)     |
|---------------------|-----------------|---------------------|-----------------|
| RCT                 |                 |                     |                 |
| Cassel 2003         | MMSE ≤2 point decline | Day 1 postop | 1.13 (0.60, 2.11) |
| Kamalian 2003       | CAM             | Day 1-2             | 0.81 (0.18, 3.60) |
| Kamalian 2003       | CAM             | Day 2-3             | 2.73 (0.12, 6.39) |
| Neuman 2016         | CAM             | Day 1-2             | 0.60 (0.29, 1.26) |
| Porter & Griffiths 2015 | Unclear               | Clear              | 0.14 (0.01, 2.64) |
| Prospective         |                 |                     |                 |
| Bitach 2006         | MMSE ≥4 point decline | Day 2-7          | 1.23 (0.58, 2.62) |
| Björkland et al. 2010 | OBS ≥ DSM IV     | After 6 hours       | 0.39 (0.36, 1.09) |
| Ilango 2016         | Clinical judgement + behabs | Anytime during | 0.86 (0.70, 1.06) |
| Retrospective       |                 |                     |                 |
| Kim 2013            | DSM IV          | Within 30 days      | 1.17 (0.72, 1.90) |
| Luger 2014          | DSM IV          | Not specified       | 1.47 (0.80, 3.02) |
| Luger 2014          | DSM IV or UCC   | Not specified       | 1.30 (0.85, 1.87) |
| Shih 2017           | Unclear         | Before discharge    | 8.04 (0.73, 49.59) |

RR>1 favours regional anaesthesia
For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

![Diagram showing comparison of study designs and anaesthesia types with WMD (95% CI) values.]

**Study** | **Study design** | **Anaesthesia type** | **No. GA** | **No. RA** | **WMD (95% CI)**
--- | --- | --- | --- | --- | ---
RCT | Perker 2015 | RCT | Spinal | 164 | 158 | -0.30 (-3.39, 2.79)
--- | Chu 2015 | Retrospective | Nerve block | 52,044 | 52,044 | 0.33 (0.24, 0.42)
--- | Le-Wenning 2012 | Retrospective | Regional | 235 | 71 | 0.19 (0.11, 0.27)
--- | Selz 2014 | Retrospective | Regional | 6136 | 6136 | 0.10 (-0.08, 0.86)
--- | Naja 2000 | Prospective | Combined Spinal/PNB | 3C | 3C | 6.90 (4.57, 9.23)
--- | Hekimoglu Sehan 2012 | Retrospective | Spinal & Epidural | 67 | 118 | -0.28 (-2.79, 2.23)
--- | Le Liu 2014 | Retrospective | Peripheral nerve block | 72 | 145 | 0.57 (0.19, 1.94)
--- | Rashid 2013 | Retrospective | Regional | 107 | 87 | 0.72 (-1.16, 2.60)
--- | Sykora 1988 | Retrospective | Epidural | 201 | 142 | 8.20 (5.21, 11.19)

**WMD >0 favours regional anaesthesia**

252x201mm (300 x 300 DPI)
Appendix A: Example of search strategy

1  exp Hip fracture/
2  hip fracture.mp.
3  (fracture$ adj2 (hip or femur$ or femor$)).tw.
4  or/1-3
5  exp an$esthesia/
6  an$esthesia.mp.
7  (anesthe$ or anaesthe$).tw.
8  an$ethetic.mp.
9  exp anesthetics/
10 exp general an$esthesia/
11  general an$esthesia.mp.
12  Anesthesia/ (43366)
13  exp Anesthesia, General/
14  general an$esthesia.mp.
15  sedation.mp. (28516)
16  exp regional an$esthesia/
17  regional an$esthesia.mp.
18  peripheral an$esthesia.mp.
19  central blockade.mp.
20  central block.mp.
21  exp spinal an$esthesia/
22  spinal an$esthesia.mp.
23  exp epidural an$esthesia/
24  epidural an$esthesia.mp.
25  exp local an$esthesia/
26  local an$esthesia.mp.
27  infiltrative an$esthesia.mp.
28  peripheral nerve block.mp.
29  intravenous regional an$esthesia.mp.
30  systemic local an$esthesia.mp.
31  exp nerve block$/
32  nerve block$.mp.
33  neuroaxial blockade.mp.
34  Anesthesia/ or exp Anesthesia, Intravenous/
35  exp inhalation an$esthesia/
36  inhalation an$esthesia.mp.
37  or/5-36
38  4 and 37
### Appendix B: Table of eligible on-going studies

| Title                                                                 | ID         | Comparison                                      | Status                 | Design                                | Contact            | Country    |
|----------------------------------------------------------------------|------------|-------------------------------------------------|------------------------|---------------------------------------|--------------------|------------|
| ClinicalTrials.gov                                                   | NCT03318133| General vs Combined lumbar plexus and sacral plexus block (CLSB) | Not yet recruiting patients | Double blind randomised trial        | Xiaofeng Wang      | China      |
| Comparison of Combined Lumbar and Sacral Plexus Block With Sedation Versus General Endotracheal Anesthesia on Postoperative Outcomes in Elderly Patients Undergoing Hip Fracture Surgery (CLSB-HIPELD): Rationale and Design of a Prospective, Multicenter, Randomized Controlled Trial | NCT03116490| General vs Regional                              | Recruiting patients        | Prospective observational cohort    | Ting Li           | China      |
| The Comparative Effects of Regional or General Anesthesia on the Prognosis of Hip | NCT03116490| General vs Regional                              | Recruiting patients        | Prospective observational cohort    | Ting Li           | China      |
| Fracture Surgery on Elderly Patients | Variations in Anaesthesia care for hip fracture surgery | NCT02787031 | General vs Neuraxial | Recruitment completed but no results available | Retrospective observational cohort | Ottawa Hospital Research Institute | Canada |
|-------------------------------------|--------------------------------------------------------|-------------|---------------------|---------------------------------------------|--------------------------------|--------------------------------|--------|
| Regional versus general anaesthesia for promoting independence after hip fracture | NCT02507505 | General vs Regional | Recruiting patients | Double blind randomised trial | Mark Powell/ Mark Neuman | USA |
| Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery | NCT02213380 | General vs Regional | Recruiting patients | Open label randomised controlled trial | Ting Li/ Sishi Chen | China |
| The safety of anaesthesia management for traumatic hip surgery in elderly | NCT02692989 | General vs Regional | Ongoing, but not recruiting patients | Retrospective observational cohort | Subhi M Alghanem | Jordan |
| Anaesthesia and post-operative mortality after proximal femur fractures | NCT02406300 | Peripheral nerve block/ General vs Subarachnoid anaesthesia | Enrolling patients by invite only | Double blind randomised controlled trial | Raul Carvalho | Portugal |
| Study Title                                                                 | Trial Identification | Comparison                        | Enrollment Status                  | Study Design          | Principal Investigator | Country       |
|----------------------------------------------------------------------------|----------------------|-----------------------------------|-----------------------------------|-----------------------|------------------------|---------------|
| Effect of anaesthesia in fracture healing                                  | NCT02621255          | General vs Regional               | Recruiting patients              | Double blind randomised trial | Ebru Biricik          | Turkey        |
| Mortality following surgery for proximal femoral fractures                 | NCT01807039          | General vs. Subarachnoid anaesthesia | Study has been completed        | Retrospective observational cohort | Petr Štourač         | Czech Republic |
| Hypobaric Lateral Spinal Anesthesia Versus General Anesthesia: Hemodynamic Stability and Short Term Cardiovascular Complications in Elderly Patients Undergoing Hip Fracture Surgery. | NCTNCT03373864       | General vs Hypobaric lateral spinal | Recruiting patients             | Randomised controlled trial | Claire Delsuc       | France        |
| Effects of different anesthesia methods on postoperative complications and hospital mortality in elderly patients | ChiCTR-RRC-17013545 | General vs Regional               | Recruiting patients              | Prospective cohort      | Xu Mao                | China         |
| Title                                                                 | ISRCTN              | Condition                  | Status                  | Type                        | Country         | Unit         |
|----------------------------------------------------------------------|---------------------|----------------------------|-------------------------|-----------------------------|-----------------|-------------|
| Hemodynamic effects of general and spinal anaesthesia for hip fracture surgery | IRCT201308316280N4  | General vs Spinal          | Completed               | Double blind randomised trial | Mohammad Haghighi | Iran        |
| A Feasibility Randomised Controlled Trial to compare Regional versus General Anaesthesia in Reducing Delirium in patients with Hip Fractures | ISRCTN15165914     | General vs Regional        | Recruiting patients    | Randomised controlled trial  | Joyce Yeung    | UK          |
## PRISMA 2009 Checklist

| Section/topic | # | Checklist item                                                                                                                                                                                                 | Reported on page # |
|---------------|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| **TITLE**     |   |                                                                                                                                                                                                             |                   |
| Title         | 1 | Identify the report as a systematic review, meta-analysis, or both.                                                                                                                                              |                   |
| **ABSTRACT**  |   |                                                                                                                                                                                                             |                   |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2,3               |
| **INTRODUCTION** |  |                                                                                                                                                                                                             |                   |
| Rationale     | 3 | Describe the rationale for the review in the context of what is already known.                                                                                                                                  | 5,6               |
| Objectives    | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).                                                   | 6                 |
| **METHODS**   |   |                                                                                                                                                                                                             |                   |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.                                              | 6                 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.                             | 6                 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.                                        | 6                 |
| Search        | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.                                                                                | Appendix A       |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).                                                       | 7                 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.                                               | 7                 |
| Data items    | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.                                                                      | 8                 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 23-27 flexible    |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).                                                                                                                                   | 8                 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.                                                          | 8                 |
## PRISMA 2009 Checklist

### Section/topic | Checklist item | Reported on page #
--- | --- | ---
Risk of bias across studies | 15 Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 23-27

### RESULTS

#### Study selection
- 17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8, Figure 1

#### Study characteristics
- 18 For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 18-22

#### Risk of bias within studies
- 19 Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 23-27

#### Results of individual studies
- 20 For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 2a/b, 3, 4, Figure 2, 3

#### Synthesis of results
- 21 Present results of each meta-analysis done, including confidence intervals and measures of consistency. | NA

### DISCUSSION

#### Summary of evidence
- 24 Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13, 14

#### Limitations
- 25 Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15, 16

#### Conclusions
- 26 Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 16

### FUNDING

#### Funding
- 27 Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 16

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The effect of regional versus general anaesthesia on post-operative delirium in elderly patients undergoing surgery for hip fracture: a systematic review

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ABSTRACT

Objective
Older patients with hip fractures who are undergoing surgery are at high risk of significant mortality and morbidity including post-operative delirium. It is unclear whether different types of anaesthesia may reduce the incidence of post-operative delirium. This systematic review will investigate the impact of anaesthetic technique on post-operative delirium. Other outcomes included mortality, length of stay, complications and functional outcomes.

Design
Systematic review of randomised controlled trials and non-randomised controlled studies.

Data Sources
Bibliographic databases were searched from inception to June 2018. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of relevant articles were checked, and clinical trial registers were searched to identify on-going trials.

Eligibility criteria
Studies were eligible if general and regional anaesthesia were compared in patients (aged 60 and over) undergoing hip fracture surgery, reporting primary outcome of post-operative delirium and secondary outcomes of mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life. Exclusion criteria were anaesthetic technique or drug not considered current standard practice; patients undergoing hip fracture surgery alongside other surgery and uncontrolled studies.

Results
One hundred and four studies were included. There was no evidence to suggest that anaesthesia type influences post-operative delirium or mortality. Some studies suggested a small reduction in length of hospital stay with regional anaesthesia. There was some evidence to suggest that respiratory complications and intraoperative hypotension were
more common with general anaesthesia. Heterogeneity precluded meta-analysis. All findings were described narratively and data were presented where possible in forest plots for illustrative purposes.

**Conclusions**

Whilst there was no evidence to suggest that anaesthesia types influences post-operative delirium, the evidence base is lacking. There is a need to ascertain the impact of type of anaesthesia on outcomes with an adequately powered, methodologically rigorous study.

This review is registered with PROSPERO (CRD42015020166).
STRENGTHS AND LIMITATIONS OF THIS STUDY

- This systematic review provides an update to evidence that examines whether the type of anaesthesia affects the development of post-operative delirium in patients with hip fractures.
- The review included randomised and non-randomised studies that included one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK.
- Other outcomes were mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
INTRODUCTION

There are an estimated 70 000-75 000 hip fractures in the UK each year with an annual cost of £2billion. [1] This is projected to rise and reach 100 000 patients a year and costing £3.6-5.6billion by 2033. [2]

Patients undergoing hip fracture surgery are often frail with inter-current illness [3] and are at risk of mortality and significant morbidity. In 2014, the National Hip Fracture Database reported 30-day mortality as 7.5%. [4] Following surgery, adverse outcomes can include delirium, myocardial infarction, pneumonia, and cerebrovascular accident. [5]

Delirium is a common neuropsychiatric syndrome defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM V) as the disturbance of attention, awareness and cognition which develops over a short period of time, represents a change from baseline and tends to fluctuate during the course of the day. [6,7] Post-operative delirium has been reported to affect between 32%-53.3% of patients and is associated with prolonged hospital stay, discharge to care homes, difficulty in regaining function in activities of daily living and increased risk of development of cognitive dysfunction and dementia in the future. [8–13] The aetiology of delirium is multifactorial, with both modifiable and non-modifiable risk factors. [14,15] There is no known treatment for delirium, however a careful approach in the peri-operative period may reduce its incidence and severity. [6,9,15–18] Guideline committees have cautiously recommended that regional anaesthesia should be given unless contraindicated. [1,9,19] Despite this, the type of anaesthesia administered in patients with hip fractures remains varied. [4]

Ninety-eight percent of patients with hip fracture are offered surgery and will require anaesthesia. [5] Anaesthesia can be broadly classified into general (GA) or regional anaesthesia (RA). RA uses neuraxial blocks that avoid the use of GA drugs and opiates which have been linked to post-operative delirium. [3] Excessive depth of anaesthesia and perioperative hypotension have been reported in GA patients and are both associated with
an increased risk of mortality. [20] However, the risk of perioperative hypotension and sedation is not completely eradicated with RA. [21,22]

Findings from previous systematic reviews looking at the effects of type of anaesthesia on post-operative outcomes in hip fracture patients are broadly suggestive of improved outcomes [3,5,23,24] and reduced incidence of post-operative delirium in patients having RA. [3,5,22,25,26] However some studies included in these reviews reported use of outdated anaesthetic drugs that are no longer relevant to current clinical practice. [5,24] Further limitations were the inclusion of only randomised controlled trials, [3,5,23,24] lack of focus on delirium as a primary outcome, [3,5,22,24,26] a limited search strategy [22] and restrictive selection criteria (e.g. exclusion of studies with patients with cognitive impairment). [23,25,26] Inadequate exploration of heterogeneity relating to delirium assessment and rating scales and assessment time points was also common. This systematic review aims to provide an up-to-date, comprehensive and methodologically robust analysis to examine the effect of RA versus GA on post-operative delirium and other outcomes in older patients undergoing surgery for hip fracture.

**METHODS**

The protocol for this systematic review has been published and is registered with PROSPERO (CRD42015020166). [27] A summary of the methods is outlined below. Reporting of the systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [28]

**Search strategy and selection criteria**

Bibliographic databases (Embase, MEDLINE, CINAHL and the Cochrane Library (CENTRAL)) were searched from inception to June 2018 using a combination of index terms and keywords relating to the population, intervention and comparator (see Appendix A for sample search strategy). There was no restriction by search date, study design or language. Web of science and ZETOC databases were searched for conference proceedings. Reference lists of
relevant articles were checked, and clinical trial registers (www.clinicaltrials.gov, www.isrctn.com and http://www.who.int/ictrp/en/) were searched to identify on-going trials. (Appendix B) Endnote 7 (Thomson Reuters) was used to store records and facilitate screening.

**Study selection**

Studies were eligible for inclusion if they met the following pre-defined criteria:

1) Population - patients aged \( \geq 60 \) years (or with a majority \( \geq 60 \) undergoing surgery for fragility hip fracture.
2) Intervention and comparator – one or more types of regional versus one or more types of general anaesthesia provided they are in current use as described in the UK. [19]
3) Outcomes – primary outcome: post-operative delirium (any criteria as defined by study authors); secondary outcomes: mortality, length of hospital stay, adverse events, functional outcomes, discharge location and quality of life.
4) Randomised or non-randomised controlled studies (prospective or retrospective).

Exclusion criteria for the primary outcome of ‘post-operative delirium’ were: anaesthetic technique or drug not considered current standard practice (e.g. outdated anaesthesia agents - halothane, enflurane, xenon); patients undergoing hip fracture surgery alongside other surgery (e.g. multiple trauma injuries); and uncontrolled studies. Two reviewers (RC, VP) independently screened titles and abstracts. Any disagreements were resolved with the support of JY. Reasons for exclusion were recorded at the full text stage.

**Data Extraction and Quality Assessment**

A piloted, standardised data extraction form was used to record information on study design, patient characteristics, type of surgery, anaesthesia type, and outcomes. The Cochrane Collaboration risk of bias tool [29] was used to assess the methodological quality of randomised controlled trials and the Newcastle-Ottawa scale [30] for non-randomised
studies. Full translations could not be obtained for three included studies [31–33], extracted data is therefore based mainly on numerical data and the English abstract. Data was extracted by RC and VP, with data checking by JY (for RC) and JD (for VP).

**Data analysis and synthesis**

Findings were grouped according to outcome. Where there was sufficient data, results were presented in forest plots (delirium, mortality and length of hospital stay). Results for studies not included in the forest plot were reported narratively. Effect estimates were not pooled as clinical and methodological heterogeneity was considered to be too great. Forest plots were thus used for illustrative purposes only and potential sources of heterogeneity (such as study design or timing of assessment) have been highlighted. Where studies did not report sufficient data for inclusion into a Forest plot (e.g. results reported narratively only, or a p-value only stated) results or conclusions from the study were nonetheless described in order to report the totality of the available evidence. Occurrence of delirium and mortality were reported as relative risks or odds ratios; length of stay (days) was reported as a mean difference. Adverse events were tabulated, where possible, according to the post-operative morbidity survey (POMS) criteria. [34] Findings for other outcomes (functional outcomes, quality of life, and discharge location) were reported narratively as heterogeneity and/or a paucity of data precluded representation in forest plots. Formal sensitivity analysis according to study quality, and assessment of publication bias using funnel plots were not possible.

**Patient and Public Involvement**

This systematic review is part of a programme of research looking at impact of anaesthesia on post-operative delirium. The research programme has received input from patient partner and Clinical Research Ambassador Group at Heart of England NHS Foundation Trust.

**RESULTS**
Of 4859 citations screened, 104 studies met the eligibility criteria (Figure 1). There were 7 randomised controlled trials (RCTs), 34 prospective and 63 retrospective controlled studies.

Twenty-two studies reported delirium (5 RCTs, [35–39] 9 prospective [18,40–47] and 8 retrospective studies [48–55]; 58 studies reported mortality (2 RCTs, [35,38] 12 prospective [42,45,56–65] and 44 retrospective studies [4,20,21,31,32,48,51,52,54,66–100]); 25 studies reported length of hospital stay (2 RCTs, [36,38] 6 prospective, [42,45,58,101–103] and 17 retrospective studies [21,51,57,68,70,71,75,78,80–83,95,104,105,98,99]); 27 studies reported adverse events (4 RCTs [35,36,39,106] 7 prospective [42,43,45,58,101,107,108] and 16 retrospective studies [20,21,48,51,52,68,69,71,75,79–81,95,96,109,110]); 11 studies reported functional outcome (3 RCTs, [35,36,111] 4 prospective [42,45,103,112] and 4 retrospective studies [62,73,105,113]) and 5 studies reported discharge location (2 prospective [43,114] and 3 retrospective studies [21,48,99]).

Thirteen potentially relevant ongoing trials were identified, with three (ISRCTN15165914, NCT03318133 and NCT02213380) planning to measure delirium post-operatively (Appendix B). No interim data was available.

Study, population and intervention characteristics
Given the large number of studies identified, only the 22 studies reporting the primary outcome of post-operative delirium have been described in detail (Table 1).

Primary Outcome

Post-operative delirium
Fifteen studies (4 RCTs [36-39], 6 prospective studies [18, 41- 45] and 5 retrospective studies [22, 48, 51, 52, 54] reporting unadjusted results are represented in the forest plot (Figure 2). Of these 15 studies, only one study found a statistically significant benefit in favour of general anaesthesia [52] and overall there was no evidence of a benefit of one type of anaesthesia over another. Seven studies were not included in forest plot due to insufficient...
data with five studies [40, 46, 47, 50, 53] reported only as abstract, one RCT [35] did not report delirium as dichotomous outcome and one retrospective study [55] only included patients who developed delirium post surgery. Only two studies compared delirium according to anaesthetic types. One retrospective study that only included patients with delirium found GA to be a significant risk factor for immediate delirium (within 24hrs of surgery) compared to RA but GA was not associated with delayed delirium (after 24hrs post surgery). [55] A further study reported as abstract also found that delirium was more common with GA, but this did not remain statistically significant on multivariable analysis. The assessment tool for delirium was not stated. [47]

Overall, there was substantial heterogeneity across the 22 studies regarding assessment tools, assessment time-points and anaesthetic protocol. Many assessment tools were poorly defined. Only 7 out of 22 studies used either DSM-IV criteria [18,40,49,53,54] or AMT. [35,50] Delirium or cognitive impairment was frequently not a primary outcome, but listed as one of several complications.

None of the RCTs that were quality assessed reported all relevant details (Table 2a). Details were lacking on the delirium assessment tools used [38] and method of randomisation. [35,36,38,39] Blinding of outcome assessment was either not undertaken [38] or unclear. [36] There appeared to be no loss to follow-up in three RCTs [36,38,39], but this was unclear for the other RCT. [35] The RCT by Kamitani was not quality assessed as a full translation was not available. [37]

The observational studies were generally considered to be at low risk of bias in terms of patient eligibility, however most had no details on blinding of outcome assessors and the level of completeness of data (Table 2b). There was variation in reporting and adjustment of potential confounding factors such as ASA score, age, gender, co-morbidities, surgery type, time to surgery and physical function. There were no details on characteristics of patients who completed follow up compared with those lost to follow up. There was also a general lack of detail on the type of assessment tool used and/or where the cut-off for a “positive” diagnosis of delirium was.
Secondary outcomes

Mortality

Two RCTs reported mortality (Table 3). One found a small and statistically significant survival benefit at 120 days and one year for GA; but no such benefit was evident at 30 or 90 days follow-up. [38] Ten observational studies reported adjusted results or results based on a matched analysis (Table 3). Two of these [20,68] found a statistically significant benefit in favour of RA for in-hospital mortality. The remaining eight studies found no significant differences. There was a lack of consistency across studies in terms of number and type of variables included in models.

Of the remaining 46 studies (results not shown) reporting unadjusted mortality results only, six [56,60,67,73,74,76] found statistically significant results in favour of RA. The remainder found no statistically significant differences or benefit comparing RA with GA.

Overall there is a paucity of good quality evidence evaluating mortality, with only one good quality RCT [38] suggesting benefit from GA at later, but not earlier time points.

Length of hospital stay

Twenty-five [21,36,38,42,45,51,57,58,68,70,71,75,78,80–83,95,98,99,101–105] studies reported length of hospital stay; nine could be included in a forest plot (Figure 3). There was no difference in length of hospital stay based on one RCT. [38] Three retrospective studies [21,68,81] compared patients with propensity score matching and showed a slight benefit towards a shorter length of stay with RA; whilst this was statistically significant in two studies, [21,68] the absolute reduction was small (up to around a third of a day). Results from the studies reporting unadjusted results were inconsistent, with three finding no difference, [71,75,80] and two finding a benefit from RA. [82,101]
Data was not available from the remaining sixteen studies due to lack of data (3 studies [57, 70, 98] were abstracts only, 6 studies [36, 42, 78, 99, 104, 105] did not provide raw data, 2 studies [45, 95] did not linked data with types of anaesthesia, and 5 studies [51, 58, 83, 102, 103] only provided median length of stay). The RCT [36] and the five prospective studies [42, 45, 58, 102, 103] did not show any significant differences. Results from the ten retrospective studies were also inconsistent: three studies [57, 70, 83] reported no difference, four studies [51, 78, 104, 99] found a statistically significant benefit for and one study [95] reported a statistically significant benefit for GA. Fukuda et al reported a statistically significant effect in favour of spinal anaesthesia, but this effect was lost after propensity score matching. [105] One large study (Nishi, n=16,687) reported in abstract form only reported a slightly shorter LOS with RA; it was unclear if this was statistically significant.[98]

Most studies reported mean length of stay, but some also reported the median, which may be more appropriate. Of twelve studies [21, 36, 45, 51, 57, 70, 71, 83, 95, 102, 103, 99] reporting the median, nine studies [21, 36, 45, 57, 70, 71, 83, 102, 103] found no statistically significant differences. Three studies found a statistically significant difference in medians, two of which favoured RA [51, 99] and one favoured GA [95].

**Adverse Events**

Twenty-seven studies reported adverse events (Table 4). There were many gaps in reporting of POMS adverse events, and it is uncertain whether this reflects non-occurrence or non-reporting of such events. Most commonly reported adverse events were pulmonary (10 studies) [20, 21, 35, 45, 48, 49, 62, 69, 89, 91] and cardiovascular events (9 studies) [21, 35, 39, 48, 58, 68, 69, 81, 95] For pulmonary events, six studies found no statistically significant differences. [35, 45, 49, 69, 89, 91] Four studies found a statistically significant difference in favour of RA (fewer cases of ventilatory support [68], respiratory failure [20, 68] and ‘overall pulmonary’ adverse events [20, 51]). There were no differences in occurrences of pneumonia [35, 48, 52, 95] or hypoxia. [75, 101] The most commonly reported cardiovascular adverse events were myocardial infarction [39, 48, 68, 95] and thromboembolic events. [35, 58, 69, 81, 95] No differences were found for myocardial
Three studies [69,81,95] reported higher incidence of thromboembolic events in GA group. Nine studies summarised overall adverse events with the majority finding no differences between the types of anaesthesia. Where there was a significant difference, this was in favour in RA (e.g. fewer incidences of ‘all complications’, [51,69] ITU admissions, [68] stroke [68] or requirement for blood transfusion). Three studies [106,108,109] found higher incidences of hypotension in the GA group.

The results are thus suggestive of a lower incidence of post-operative respiratory, cardiac and overall complications in the RA group. However, reporting of adverse events, including methods of ascertainment, was inconsistent and limited.

**Functional outcomes**

Eleven studies reported functional outcomes using a variety of outcome measures. Two RCTs reported a significantly quicker time to ambulation in the RA group (3.3 days RA vs 5.5 days GA). [35] and a statistically significant earlier discharge time from PACU (post-anaesthesia care unit) in the RA group (RA 15 (5-30) min vs. GA 55 (15-80) min, p=0.0005) [36]. However one RCT found that patients given RA was slower to be discharged from PACU (Mean time to discharge GA 35.04min (SD 3.39) vs RA 41.26min (SD 8.37), p=0.001).[111] No significant differences were found in the non-randomised studies regarding time to ambulation, [103,112,113] walking speed, [62] time to rise from chair, [42] mean Barthel’s score [73] or ambulation at 3, 6 and 12 month post-surgery. [45,105] Overall results may suggest a small benefit from RA for immediate post-anaesthetic mobilisation. However, the evidence is limited by small sample size, unknown method of outcome assessment and blinding of assessors.

**Discharge location**
Five non-randomised studies described discharge locations of patients following hip fracture. [21,43,48,99,114] One study with only 14 patients reported that more patients returned home in the RA group [45]. A large retrospective study reported lower odds of returning to home residence and higher chance of admitting to healthcare facility in GA group compared to RA (16695 patients, return home adjusted OR 0.91 (95%CI 0.84, 0.97); healthcare facility admission OR 1.10 (95%CI 1.03, 1.19). [99] A cohort study of 4815 patients found operation under GA significantly increased risks of rehabilitation admission instead of home (adjusted OR 1.74, 95%CI 1.34, 2.25, p<0.001). [114] However, two larger studies [21,109] found no difference in discharge location between GA or RA groups.

**Quality of Life**

There were no studies that evaluated the effect of type of anaesthesia on quality of life in patients after hip fracture surgery.

**DISCUSSION**

For the primary outcome of post-operative delirium, this systematic review did not find any difference between types of anaesthesia. Furthermore, no survival benefit could be demonstrated with either type of anaesthesia up to one year post-operatively. A small number of studies suggested that fewer adverse events might be associated with RA. Similarly some studies were suggestive of a small reduction in hospital stay with RA. Data was limited for functional outcomes and discharge data. Two small RCTs suggested a benefit from RA for immediate post-anaesthetic mobilization. There were no studies that reported on quality of life after different types of anaesthesia.

This is the most comprehensive and methodologically robust systematic review to date. It includes both RCTs and non-randomised controlled studies, focusing on delirium as a primary outcome as well as synthesising findings for a range of other important outcomes including adverse events. Results for RCTs, non-randomised studies, adjusted and
unadjusted results were presented and considered separately. It was anticipated that non-randomised studies, which are more prone to bias, may overestimate effect sizes compared with RCTs. No such trends were observed however, as studies of any design mostly showed no difference in effect.

A sensitive search strategy means it is unlikely that many studies would have been missed. Careful consideration of heterogeneity has meant that no meta-analyses were undertaken, but results were presented in forest plots where possible to show the overall direction of effect and heterogeneity between studies.

Delirium can be diagnosed using the criteria from the DSM-V or the WHO’s ICD-10 classification of diseases. [7,115] However in clinical practice the criteria can be difficult to apply [116] and tools such as the confusion assessment method (CAM), Delirium Rating Scale revised-98 (DRS-R-98), Neelon and Champagne (NEECHAM) confusion scale [117] or 4AT have been advocated as validated screening tools. (4 ‘A’s’ Test) [6,116,118] No consensus exists in the literature as to which tool should be the gold standard. [6,119,120] The accurate assessment of delirium can be affected by the presence of pain and residual drugs in the immediate period following surgery therefore timing of assessment is also important. [121] No significant differences were found for the incidence of post-operative delirium, based on four RCTs and 14 non-randomised studies but there were significant differences in the assessment tools and the assessment time-points. Most of the RCTs were small and most likely underpowered. In the largest RCT [38] delirium was not a primary outcome and the assessment tool used or the timing of assessments was not reported. The pathophysiology of delirium remains poorly understood but there are a combination of pre-existing and precipitating factors that can pre-dispose the patient to post-operative delirium. [11,122,123] Pre-existing patient risk factors including age > 70 years, pre-existing cognitive impairment, history of post-operative delirium, visual impairment, cerebrovascular disease and renal impairment [124,125] are associated with higher risk of delirium. Precipitating factors can include acute injury such as a hip fracture, malnutrition, electrolyte imbalance and the use of urinary catheter and physical restraints. [125] Specific perioperative risk factors include intraoperative blood loss, post-operative transfusions and severe acute pain.
The studies that adjusted for confounders and reported delirium [40,42,52,53] found no association between type of anaesthesia and post-operative delirium. Confounders adjusted for included demographics, ASA classification, co-morbidities, nutritional status, fracture type, pre-operative blood transfusion and readmission. However, with multifactorial risk factors for delirium, it is difficult to encompass all variables. Other important characteristics such as anaemia, time to surgery, blood loss, intra-operative hypotension and sedation, can also influence outcome but were less frequently included as variables. Given the lack of consistency across studies in terms of number and type of variables included in models and the reporting of these, it is not possible to gauge the overall impact that adjusting for confounders may have on the direction of effect.

There were limitations in the primary data included in this systematic review. There were a limited number of RCTs (3% of total number of patients included for the primary outcome) and many of the non-randomised studies did not make any attempts to adjust for potential confounding factors. When confounding variables were considered, this was often done for mortality only. There was significant heterogeneity across studies in study design, population age, comparators, assessment time-points and definition of outcomes (particularly delirium) that precluded quantitative pooling.

Detailed reporting of anaesthetic techniques was suboptimal especially for GA techniques. RA techniques employed were more commonly reported, but the specific drugs used were not described. Opioids are known to cause delirium [3,128] and acute pain is a well-recognised precipitating factor of delirium but both were poorly reported. Whilst most studies planned to collect adverse events data, it was unclear whether adverse events were predetermined. Small sample sizes (n<30) and rare occurrences of adverse events means that many studies were likely underpowered. [35,36,48,101]. The style of data reporting in included studies could also lead to over-reporting of complications; for example, a patient could develop pneumonia, which led to respiratory failure and the need for inotropic and ventilatory support and ITU admission. Thus five adverse events would be attributable to a single patient, but this may not be evident from the data. Incidence of intraoperative
hypotension was not captured by POM categories, as inotropic support use was not reported. Hypotension can lead to hypoperfusion and organ damage. A recent analysis of data from an audit of outcomes in hip fracture patients demonstrated increased risk of death associated with intraoperative hypotension. In our review, three studies [106,108,109] examined hypotension all of which found higher incidences of hypotension in the GA group. Four studies [52,69,106,109] also found significantly higher volumes of fluids and blood products transfused in the GA group.

Subgroup analysis was not feasible and no individual studies reported findings for different sub-groups. It is possible that there are some patients who may, in some circumstances, benefit from RA compared to GA that have not been captured by the evidence presented in this systematic review. Subgroup analysis of specific at risk patients, for example the frail and the very elderly, may suggest a benefit for either regional or general anaesthesia in certain population groups.

Older patients are at high risk of adverse outcomes post-operatively due to age-related physiological decline, multiple co-morbidities and polypharmacy. [129] Principles of care for older patients in the peri-operative setting should employ an anaesthetic technique that leads to rapid recovery, dosing of drugs specific to individual pharmacokinetic variation and appropriate pain management strategies. [130] Most recently, the European Society of Anaesthesiology consensus-guideline on post-operative delirium also did not find substantial evidence to recommend a specific type of anaesthetic technique but advocates intraoperative monitoring to avoid swings in blood pressure and excessive depth of anaesthesia. [131] Given the lack of standardised assessment tools of delirium and the paucity of suitably powered, methodologically sound studies, uncertainty remains regarding any potential benefits of certain types of anaesthesia. However, even a modest reduction in adverse events and length of hospital stay could benefit many patients and result in cost savings for health care providers. Future research examining post-operative delirium should include robust assessment and diagnosis of delirium. There is also an urgent need for high quality research comparing anaesthetic techniques that focus on patient-related outcomes such as quality of life and functional outcomes.
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Author Contributions
All authors have made substantial contributions to the manuscript. JY: the conception and design of the study, VP/RC/JD/JY acquisition of data, analysis and interpretation of data, VP/RC/JD/JY drafting the article or revising it critically for important intellectual content, VP/RC/JD/JY final approval of the version to be submitted. We would like to thank Mrs Preeti Pulgari for her assistance with the review.

Data sharing statement
There are no unpublished data from this review.
Table 1: Table of characteristics of studies that measured postoperative delirium

| Author Year Country | ASA | Comparison and number of patients | Population | Age, mean age and M/F split | Outcomes measured |
|---------------------|-----|----------------------------------|------------|-----------------------------|-------------------|
| **RANDOMISED CONTROLLED TRIALS** |     |                                  |            |                             |                   |
| Bigler 1985 DENMARK |     | General: ASA 1: 2, ASA 2: 14, ASA 3: 4, Spinal: ASA 1: 2, ASA 2: 15, ASA 3: 3 | General (n=20) v Spinal (n=20) | Patients having acute surgery for hip fracture | Patients above 60 years of age - Postoperative mental function - Morbidity |
|                     |     |                                  |            | Mean age General: 77.6 years (SEM 2.3) Spinal: 80.1 years (SEM 1.6) M/F: 7/33 |
| Casati 2003 ITALY   |     | General: ASA 2: 7, ASA 3: 8, Spinal: ASA 2: 6, ASA 3: 9 | General (n=15) v Spinal (n=15) | Patients undergoing hip fracture repair | Patients over 65 years of age - Hypotension - Cognitive dysfunction |
|                     |     |                                  |            | Mean age General: 84 years (range 67-88) Spinal: 84 years (range 71-94) M/F: 2/28 |
| Kamitani 2003 JAPAN |     | ASA not reported. Comparable 'physical status' between GA and RA groups | General (n=21) v Spinal (n=19) | Patients with femoral neck fracture | Patients aged 70 and over - Postoperative delirium |
|                     |     |                                  |            | Mean age General: 81.4 (SD 6.2) Spinal: 83. (SD 6.0) M/F: 4/36 |
| Neuman 2016 USA     |     | No details General: ASA 2, Spinal: ASA 3 | General (n=6) v Spinal (n=6) | Femoral neck or pertrochanteric hip fracture surgery | Patients aged 18 and over - Postoperative delirium |
|                     |     |                                  |            | Median age(GA): 62.5 (57-88) Median age (RA): 80.5 (62-92) |
|                     |     |                                  |            | Primary: Secondary: |
| Feasibility study/Letter | General: ASA Grade 1 or 2: 98  Spinal: ASA Grade 1 or 2: 94.9 | Patients with acute hip fracture | M/F: 9/3 | Mortality
---|---|---|---|---
Parker & Griffiths 2015 UK | General (n=164) v Spinal (n=158) | Patients over 49 years of age Mean age General: 83.0 years (range 59-99) Spinal: 82.9 years (range 52-105) M/F: 87/235 | Primary: Mortality Secondary: Surgical outcomes General complications Hospital stay

### PROSPECTIVE STUDIES

| Atay 2012 TURKEY | Unable to obtain full translation. | Patients with hip fractures Mean age M/F: | Patients aged 60 years and over Mean age M/F: | Postoperative delirium Postoperative cognitive function
---|---|---|---|---|---
Bitsch 2006 DENMARK | ASA 1=2 ASA 2=33 ASA 3=51 ASA 4=10 | General (n=13) v Regional (n=83) | Hip fracture patients Mean age No age restriction M/F: | Risk factors for pre, intra and post-operative cognitive dysfunction
---|---|---|---|---|
Bjorkelund 2010 SWEDEN | Intervention group (new care plan): ASA 1=17 ASA 2=59 ASA 3=48 ASA 4=7 Control group (existing care plan: ASA 1=10 | General (n=89) v Spinal (n=174) | Patients with hip fractures Mean age Intervention: 81.1 years (SD 7.5) Control: 82.0 years (SD 7.6) M/F: | Incidence of Delirium
| Study       | Country | Study Design | ASA | Patients | Selection Criteria | Age | Complications | Outcome Measures                      |
|-------------|---------|--------------|-----|----------|--------------------|-----|---------------|---------------------------------------|
| Gilbert 2000 | USA     | General: ASA 1-2: 105, ASA 3-4: 194 | Spinal: ASA 1-2: 109, ASA 3-4: 309 | Patients with an acute hip fracture | Age 65 years and older | - Complications (in-hospital and surgical) | - Functioning (daily, social, mental) |
| Ilango 2015  | Australia | Not reported | General (n=167) v Spinal (n=151) | Hip fracture patients | Age not specified within inclusion criteria | - Incidence of postoperative delirium | - Other postoperative complications |
| Juliebo 2009 | Norway   | ASA 1 or 2 = 182 | General (n=20) v Spinal (n=337) | Patients with hip fracture | Patients aged 65 years and over | - Delirium | |
| Koval 1999   | USA      | General: ASA 1 or 2: 236, ASA 3 or 4: 120 | Spinal (n=280) | Patients who sustained a hip fracture | Patients 65 years of age and older | - Inpatient medical complication rate | - Hospital mortality rate |

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| Author | Year | Country | Study Design | Methodology | Patient Population | Findings |
|--------|------|---------|--------------|-------------|--------------------|---------|
| Mohamed | 2017 | UK | Abstract | ASA 1 or 2: 131 ASA 3 or 4: 137 | Total n=85 Hip fracture patients | No details. |
| Ojeda | 2018 | Spain | Abstract | No details | Total n=303 Hip fracture patients | Patients aged 70 years and over. - Delirium |
| | | | | | | Mean age 84 (SD 6) M/F: 39%/61% - In-hospital complications - Mortality |
| RETROSPECTIVE STUDIES | | | | | | |
| Bellelli | 2013 | ITALY | Abstract | Not reported | General v Spinal v Peripheral nerve block 392 included patients, but no breakdown of who received what anaesthesia Patients undergoing hip fracture surgery | Patients aged 65 years and older - Postoperative delirium |
| | | | | | | Mean age: 83 years (SD 6) M/F: Not reported |
| Choi | 2017 | Republic of Korea | For those who developed delirium: ASA 2: 10 ASA 3: 97 | Total n=356 For those who developed delirium: General (n=81) v Spinal (n=29) | Patients with femoral neck fracture | Patients aged 70 years and over - Immediate and delayed delirium |
| | | | | | | M/F: 66/290 |
| Author          | Year | Country | ASA 4: 3 | ASA 1: 6 | ASA 2: 3 | ASA 3: 189 | General (n=246) v Spinal (n=249) v Epidural (n=11) | Hip fracture surgery patients | Patients aged 60 years and over | 30 day postoperative complications | Cardiac complications | Pulmonary complications | Delirium | Death |
|-----------------|------|---------|----------|----------|----------|------------|---------------------------------------------------|-------------------------------|----------------------------------|-----------------------------------|------------------------|------------------------|----------|-------|
| Kim            | 2013 | KOREA   |          |          |          |            | General (n=246) v Spinal (n=249) v Epidural (n=11) | Hip fracture surgery patients | Patients aged 60 years and over | Age 60-69 years n=83 70-79 years n=227 >80 years n=196 | M/F: 140/366 |          |         |
| Konttinen      | 2006 | FINLAND | ASA 3: 8 |          |          | ASA 4: 6   | General (n=3) v Spinal (n=11, single shot: 5, continuous: 6) (14 procedures in 12 patients) | Patients undergoing major emergency surgery | Patients aged 100 years and over | Median age: 101 years | M/F: 2/10 |          |         |
| Luger          | 2014 | AUSTRIA | Mean ASA: Group 1 (post-op delirium): 2.9 +/- 0.6 |          |          |            | General (n=116) v Regional (n=213) | Patients scheduled for acute hip fracture surgery | Patients aged 80 years of age and older | Age Delirium: 87.9 years (SD 4.5, range 81-97) No delirium: 88.8 years (SD 5.3, range 81-100) | M/F: 19/51 |          |         |
| Michael        | 2014 | UK      | Not reported |          |          |            | General v Spinal (704 patients included in analysis, but unclear how many received which anaesthesia) | Hip fracture patients | Patients aged 60-100 years | Age 60-70 years n=50 70-80 years n=169 80-90 years n=338 90-100 years n=147 | M/F: 178/526 |          |         |

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| Study | Location | General: ASA 1 or 2 | Regional: ASA 1 or 2 | General (n=6206) v Regional (n=3219, spinal n=3078 and epidural n=141) | Hip fracture patients | Patients 60 years of age or older | Primary: -30 day mortality | Secondary: -7 day mortality | Other: -7 day morbidity |
|-------|----------|---------------------|---------------------|-----------------------------------------------------------------|-----------------------|---------------------------------|-----------------------------|-----------------------------|-----------------------------|
| O’Hara 2000 USA | | 1698 | 618 | 560 | ASA 1 or 2: 1698  
ASA 3: 3666  
ASA 4 or 5: 618  
Regional: ASA 1 or 2: 560  
ASA 3: 2097  
ASA 4 or 5: 438 | | | | | |
| | | | | | Patients 60 years of age or older | | | | | |
| | | | | | Age | | | | | |
| | | | | | General: | | | | | |
| | | | | | 60-69 years n=910  
70-79 years n=1918  
80-89 years n=2602  
90+ years n=776 | | | | | |
| | | | | | Regional: | | | | | |
| | | | | | 60-69 years n=325  
70-79 years n=881  
80-89 years n=1452  
90+ years n=561 | | | | | |
| | | | | | M/F: 2010/7415 | | | | | |
| Shih 2010 TAIWAN | | 47 | 15 | 45 | ASA 2: 47  
ASA 3: 115  
ASA 4: 1  
Spinal: ASA 2: 45  
ASA 3: 120  
ASA 4: 2 | | Patients undergoing hip fracture repair | Patients aged 80 and over | Mean age | | |
| | | | | | General: 83.96 years (SD 3.71)  
Spinal: 84.93 years (SD 4.04) | | M/F: 189/146 | -Postoperative morbidity | -Postoperative mortality | -Pre and intraoperative variables | |

ASA is American Society of Anesthesiologists Physical Status Classification System; SD is standard deviation. SEM is standard error of the mean.
### Table 2a: Quality assessment of RCT studies reporting delirium

AMT is Abbreviated mental test  
CAM is Confusion assessment method  
DRS is Delirium Rating Scale  
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition  
MMSE is Mini mental state examination

| Study          | Randomisation | Concealment of allocation | Similarity at baseline | Blinding of outcome assessor | Incomplete outcome data (for outcome of delirium) | Validity of assessment tool | Assessment tool specific for delirium | Selective reporting |
|----------------|---------------|----------------------------|-------------------------|------------------------------|-----------------------------------------------|-----------------------------|-------------------------------------|---------------------|
| Neuman 2016    | UNCLEAR       | UNCLEAR                    | Groups similar for age, gender and comorbidities. | LOW                          | LOW                                          | CAM good validity for identifying delirium | Yes                   | UNCLEAR             |
| N=12 (Letter)  | No details.   |                            |                         |                              |                                              |                             |                                     |                     |
| Parker & Griffiths 2015 | UNCLEAR       | LOW                        | Groups similar for all baseline characteristics measured, except for proportion of male patients (35% in GA group, 19% in RA group). | HIGH                          | LOW                                          | Unclear-no details           | Unclear               | UNCLEAR             |
| N=322          | Randomisation undertaken by opening sealed opaque numbered envelopes prepared by a person independent to the trial. |                         |                         |                              |                                              |                             |                                     |                     |
| Casati 2003    | UNCLEAR       | LOW                        | Groups similar for all baseline characteristics measured. | UNCLEAR                       | LOW                                          | MMSE good validity for cognitive function | No                    | UNCLEAR             |
| N=30           | Using a sealed envelope technique, patients were randomly allocated... |                         |                         |                              |                                              |                             |                                     |                     |
| Bigler 1985    | UNCLEAR       | UNCLEAR                    | Groups similar for all baseline characteristics measured except for vasopressors being administered more frequently in spinal group. | UNCLEAR                       | UNCLEAR                                      | AMT good validity for cognitive dysfunction | No                    | UNCLEAR             |
| N=40           | No details (other than “patients randomly allocated”) | No details              |                         |                              |                                              |                             |                                     |                     |

**Risk of bias described as LOW, UNCLEAR or HIGH**

NB Quality assessment was not performed for Kamitani [37] as a full translation was not available. Blinding of patients and surgeons/anaesthetists not possible.

### Table 2b: Quality assessment of observational studies reporting delirium
AMT is Abbreviated mental test
CAM is Confusion assessment method
DRS is Delirium Rating Scale
DSM-IV is Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
MMSE is Mini mental state examination

| Study                  | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------------------|----------------------|----------------------|-------------------------------|---------------------------------|---------------------------|-------------------------------|
| **Belloni 2013**       | LOW                  | HIGH for unadjusted data | UNCLEAR                      | LOW                             | Yes                       | LOW                           |
| (Abstract)             |                      | LOW for adjusted data |                               |                                 |                           | Patients with incomplete data in medical records were excluded from this study. Proportion not stated. |
| RETROSPECTIVE          | Patients aged > 65 years admitted to one orthogeriatric unit between 2007 and 2011. | Baseline characteristics not presented for anesthecia groups, but multivariable analysis for confounders (age, gender, Charlson Comorbidity Index, ASA score, pre-fracture disability in Activities of Daily Living (Katz's ADL Index), and pre-fracture dementia) | No details                     | DSM-IV-TR criteria           |                           |                               |
| **Bitsch 2006**        | UNCLEAR              | HIGH                 | UNCLEAR                       | LOW-good validity for cognitive function | No                        | HIGH                          |
| PROSPECTIVE            | Consecutive patients but large number excluded and unclear if similar characteristics to included | No baseline characteristics for groups according to type of anesthetic; no adjusted analyses. | No details | MMSE |                               |                               |
| **Björkelund 2010**    | LOW                  | HIGH                 | UNCLEAR                       | LOW                             | No for Organic Brain Syndrome Scale and DSM-IV criteria | LOW                           |
| PROSPECTIVE            | Consecutive patients included | No baseline characteristics for groups according to type of anesthetic; no adjusted analyses. | No details | Organic Brain Syndrome Scale and DSM-IV criteria | Yes for DSM-IV criteria    |                               |
| **Choi 2017**          | LOW                  | HIGH for unadjusted data | LOW                           | LOW                             | Yes                       | LOW                           |
| Study       | Eligibility criteria                                                                                                                                 | Confounders Low risk                                                                 | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|------------|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-------------------------------|---------------------------------|---------------------------|-------------------------------|
| RETROSPECTIVE | Consecutive patients included                                                                                                                                                      | Variables adjusted for were age, previous dementia, parkinsonism, ASA grade and ICU care. | Assessment made by independent psychiatrist | CAM, CAM-ICU                      | Appears to include all eligible consecutive patients. |
| Gilbert 2000  | LOW                                                                                                                                                                              | HIGH for unadjusted data; LOW for adjusted data                                      | UNCLEAR                        | LOW (MMSE) HIGH (“mental confusion”) No (MMSE) | Unclear                   | No details-only how many included in final analysis |
| PROSPECTIVE   | Patients given general and spinal were drawn from the same population                                                                                                          | Appear to be some baseline imbalances between general and regional groups, but multivariable analyses for all outcomes. Variables were age, sex, race, comorbidities, pre-fracture physical function, ASA score, fracture type, surgical procedure and physiologic status. | No details                     | Mental confusion not further defined; MMSE | UNCLEAR                    | No details-only how many included in final analysis |
| Ilango 2015    | LOW                                                                                                                                                                              | HIGH                                                                                 | UNCLEAR                        | Subjective method (“clinical judgement”) and several scales; cut-off unclear. | Unclear                   | 19/337 (6%) incomplete data. No details on characteristics. |
| PROSPECTIVE   | All hip fracture patients admitted over a year                                                                                                                                     | Similar baseline characteristics (age, gender, pre-op cognitive function), but no adjusted analyses. | No details                     | Subjective method (“clinical judgement”) and several scales; cut-off unclear. | Unclear                   | 19/337 (6%) incomplete data. No details on characteristics. |
| Juliebo 2009   | LOW                                                                                                                                                                              | HIGH                                                                                 | LOW                           | Staff performing assessments were not involved in the care of enrolled patients | LOW                        | HIGH                          |
| PROSPECTIVE   | All eligible hip fracture patients September 2005 to December 2006.                                                                                                              | Univariate analysis only for type of anaesthetic and outcome. No details on similarity of groups for this variable. Adjusted analyses not with type of anaesthetic as a variable. | LOW                           | CAM                             | No statistically significant differences between patients enrolled and not enrolled for age/sex. No details on the 79 who refused to take part. |
| Kim 2013       | LOW                                                                                                                                                                              | HIGH                                                                                 | UNCLEAR                        | LOW                             | Yes                         | LOW                           |
| Study                        | Eligibility criteria                                                                 | Confounders Low risk                                                                                                                                                                                                 | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data                                                                 |
|------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------------|---------------------------|---------------------------------------------------------------------------------------------|
| RETROSPECTIVE                | Consecutive sample of hip fracture patients                                             | No adjusted analyses including type of anaesthesia. No details on similarity of baseline characteristics for groups.                                                                                               | No details                   | DSM-IV criteria                 | UNCLEAR                   | Appears to be no missing data                                                                |
| Kontinnen 2006               | All patients over 100 years old undergoing emergency surgery in one hospital           | No adjusted analyses. No details                                                                                                                                         | No details                   | Not clearly defined             | UNCLEAR                   | No details on missing data/exclusions.                                                        |
| Koval 1999                   | Patients with hip fracture admitted to one hospital between 1987 and 95. Patient excluded if certain characteristics meant type of anaesthetic was pre-determined. | Some imbalances in baseline characteristics. Adjustment for covariates described but results presented appear to be unadjusted.                                                                                       | No details                   | Not clearly defined             | Unclear                   | 4.4% of patients lost to follow-up. No further details                                         |
| Luger 2014                   | Patients scheduled for acute hip fracture surgery at Innsbruck Medical University between 2005 and 2007 | No details on baseline characteristics between groups. No adjusted analyses.                                                                                                                                            | No details                   | “Unspecified cognitive dysfunction behaviour” and DSM-IV (unspecified) | Yes (DSM-IV)              | 82/411 (20%) excluded due to incomplete records. Unclear if excluded had different characteristics to those included |
| Michael 2014 (Abstract)      | Consecutive patients                                                                   | No details on baseline characteristics between groups. No adjusted analyses.                                                                                                                                          | No details                   | AMT                             | Yes                       | 34/738 (5%) excluded retrospectively. No reasons for exclusions.                              |
| Mohamed 2016 (Abstract)      | Patients from 6 hospitals; no further details                                           | No details on baseline characteristics between groups. No adjusted analyses.                                                                                                                                          | No details                   |                                | Unclear                   | Data from enrolled patients analysed.                                                         |
| Study       | Eligibility criteria | Confounders Low risk | Blinding of outcome assessors | Validity of Assessment tool used | Tool specific for delirium | Loss to follow up/missing data |
|-------------|----------------------|----------------------|-------------------------------|----------------------------------|---------------------------|-------------------------------|
| O’Hara 2000 | LOW                  | HIGH for unadjusted data | UNCLEAR                       | UNCLEAR                          | Unclear                   | UNCLEAR                       |
|             |                      | LOW for adjusted data |                               |                                  |                           | 9425/9598 < 2% missing       |
| RETROSPECTIVE | Consecutive patients from 20 hospitals | Appear to be some baseline imbalances between groups, but multivariable analyses. Variables were gender, history of cardiovascular disease, history of stroke, abnormal preoperative chest radiograph, type of surgical repair, age, hospital, and ASA score. | No details | Not clearly defined | Unclear | Unclear |

| Ojeda 2018 (Abstract) | UNCLEAR | HIGH for unadjusted data | UNCLEAR | UNCLEAR | Unclear | UNCLEAR |
|                       |         | LOW for adjusted data    |         |         |                           | 9425/9598 < 2% missing       |

| PROSPECTIVE | Patients over 70 years admitted with a hip fracture; no further details. | Unclear if any baseline imbalances. Variables in multivariable analysis were time to surgery, ASA status and comorbidities. | No details | No details | No details. | No details. |

| Shih 2010 | LOW | HIGH | UNCLEAR | UNCLEAR | Unclear | LOW |
| RETROSPECTIVE | Octogenarian patients undergoing hip fracture repair in one centre between 2002 and 2006. | Some baseline imbalances between groups; no adjusted analyses for delirium (only for “morbidity”) generally. | No details | Not clearly defined | Appears to be no missing data from those patients included. |

NB Quality assessment was not performed for Atay [31] as a full translation was not available.

Table 3 Mortality results
| Study                  | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI) | Adjusted/matched OR or RR (95% CI) | Note                                                                 |
|------------------------|------------|---------------------|---------------------|-----------------------------|-----------------------------------|----------------------------------------------------------------------|
| **RCTs**               |            |                     |                     |                             |                                   |                                                                      |
| Bigler 1985            | In-hospital| 1/19                | 1/19                | RR=1.00 (0.07, 14.6)        |                                   | No statistically significant difference in in-hospital mortality.    |
| Parker & Griffiths 2015| 30 day     | 8/156               | 5/153               | RR=1.54 (0.52, 4.58)        |                                   | No statistically significant difference in mortality at 30 or 90 days.|
| Parker & Griffiths 2015| 90 day     | 12/152              | 12/146              | RR=0.96 (0.45, 2.07)        |                                   | Statistically significant difference in mortality at 120 days and    |
|                        |            |                     |                     |                             |                                   | 1 year in favour of GA.                                              |
| Parker & Griffiths 2015| 120 day    | 12/152              | 15/143              | RR=0.77 (0.61, 0.91)        |                                   |                                                                      |
|                        | 1 year     | 19/145              | 32/126              | RR=0.57 (0.34, 0.96)        |                                   |                                                                      |
| **Prospective cohort** |            |                     |                     |                             |                                   |                                                                      |
| Withey 1995            | 1 year     | Total only reported:303 | Total only reported:161 | Not reported.              | OR 1.28 (0.76, 2.14)            | No statistically significant difference in mortality (adjusted data).|
| Zhao 2015              | Unknown    | 65/166              | 22/238              | Not reported.              | OR 0.687 (0.248, 1.906)         | No statistically significant difference in mortality (adjusted data).|
| **Retrospective cohort**|            |                     |                     |                             |                                   |                                                                      |
| Chu 2015               | In-hospital| 1363/50681          | 1107/50937          | Not reported.              | OR 1.24 (1.15, 1.35)            | Statistically significant difference in mortality (adjusted data) in favour of RA.|
| Neuman 2012            | In-hospital| 325/12579           | 110/5144            | Not reported.              | OR 0.710 (0.541, 0.932)         | Statistically significant difference in in-hospital mortality in favour of RA (OR<1 indicates benefit from RA). |
| Patorno 2014           | In-hospital| 1477/66345          | 144/6939            | RR 0.94 (0.79 to 1.11)     | RR 0.93 (0.78 to 1.11)          | No statistically significant difference in mortality (adjusted or unadjusted). |
| O'Hara 2000            | 7 day      | 82/6124             | 53/3076             | OR 0.80 (0.56-1.13)        | OR 0.90 (0.59-1.39)             | No statistically significant difference in mortality (adjusted or unadjusted). |
| Basques 2015           | 30 day     | 450/6803            | 166/2423            | 0.97 (0.81 to 1.17)        | OR 0.98 (0.82 to 1.20)          | No statistically significant difference in mortality (adjusted or unadjusted). |
| O'Hara 2000            | 30 day     | 272/5934            | 174/2955            | OR 0.80 (0.66-0.97)        | OR 1.08 (0.84-1.38)             | No statistically significant difference in mortality (adjusted or unadjusted). |
| Qiu 2018               | In hospital| 226/9629            | 111/6597            | Not reported.              | HR 1.38 (1.10-1.73)             | No statistically significant difference in mortality                 |
| Seitz 2014             | 30 day     | 1044/7774           | 1450/10705          | RR 0.99 (0.92, 1.07)       | RR 1.04 (0.94, 1.15)            | No statistically significant difference in 30 day mortality (matched or unmatched). |

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| Study       | Time-point | Deaths/no deaths GA | Deaths/no deaths RA | Unadjusted OR or RR (95% CI) | Adjusted/matched OR or RR (95% CI) | Note                                                                 |
|-------------|------------|---------------------|---------------------|-----------------------------|-----------------------------------|----------------------------------------------------------------------|
| Whiting 2015| 30 day     | Total only stated: 5840 | Total only stated: 1924 | Not reported.               | Spinal and regional nerve blocks  |
|             |            |                     |                     |                             | OR 1.18 (0.91, 1.53)              | Spinal only OR 1.20 (0.92–1.56) Regional only OR 1.22 (0.54–2.76)   |
|             |            |                     |                     |                             | No statistically significant difference in 30 day mortality (adjusted data).|

OR is odds ratio; RR is relative risk
Table 4: Summary findings table of studies reporting adverse events. *OR = Odds Ratio GA vs. RA; NR = not reported; NS = not significant

| POMS categories | Study       | Adverse event description | GA               | RA               | Summary statistic*/p-value         |
|-----------------|-------------|----------------------------|------------------|------------------|-----------------------------------|
| Pulmonary       | Basques 2015| Ventilatory support        | 58/7253 (0.8%)   | 13/2589 (0.5%)   | NR                                |
|                 |             | Pneumonia                  | 261/7253 (3.6%)  | 108/2589 (4.2%)  | NR                                |
|                 | Bigler 1985 | Pneumonia                  | 2/20             | 1/20             | NR                                |
|                 | Chu 2015    | Respiratory Failure        | 868/5204 3       | 328/5204 4       | OR 2.71 (95%CI 2.38 to 3.01), p<0.001, Favours RA |
|                 |             | Ventilatory support        | 4008/5204 43     | 338/5204 4       | OR 6.08 (95%CI 5.59 to 6.61), p<0.001, Favours RA |
|                 | Konttinen 2006 | Pneumonia             | 0/3              | 2/11             | NR                                |
|                 | Le Liu 2014 | Overall pulmonary          | 18/172 (25%)     | 27/145 (25.5%)   | P=0.934 NS                        |
|                 |             | Hypoxia                    | 19/72 (26.4%)    | 23/145 (15.9%)   | P=0.065 NS                        |
|                 | Le Wendling 2012 | Overall pulmonary     | 17/235 (6%)      | 1/73 (1%)        | OR 2.2 (95%CI 0.7 to 7.2), P=0.0841, Favours RA |
|                 | Naja 2000   | Hypoxia                    | 2/30 (6%)        | 0/30 (0%)        | NR                                |
|                 | Neuman 2012 | Overall pulmonary          | 1030/12904 (8.1%) | 359/5254 (6.8%) | P=0.005, Favours RA               |
| Cardiovascular Event | Study | Event | Number | Number of Events | OR | 95% CI | P Value | Conclusion |
|----------------------|-------|--------|--------|------------------|-----|---------|---------|------------|
| Respiratory Failure  | O'Hara 2000 | Pneumonia | 1040/12904 (5%) | 178/5254 (3.4%) | P<0.0001 | 1.21 (0.87 to 1.68) | Favours RA |
| Overall pulmonary    | Shih 2010 | 11/167 (6.6%) | 3/168 (1.8%) | P<0.03 | Favours RA |
| Myocardial infarction| Basques 2015 | 137/7253 (1.9%) | 49/2859 (1.9%) | NR |
| Thromboembolic       |         | 138/7253 (1.9%) | 25/2589 (1.0%) | NR |
| Cardiovascular       | Bigler 1985 | 1/20 | 1/20 | NR |
| Pulmonary embolism   |         | 1/20 | 1/20 | NR |
| Myocardial infarction| Chu 2015 | 188/5204 (3.06%) | 169/5204 (3.2%) | OR 1.11 (0.9 to 1.37), p=0.31 | NS |
| Thromboembolism      | Fields 2015 | 1.64% | 0.72% | P=0.004 | Favours RA |
| Myocardial infarction| Konttinen 2006 | 0/3 | 1/11 | NR |
| Myocardial infarction| Neuman 2016 | 1/6 | 0/6 | NR |
| All cardiovascular complications | Le Wendling 2012 | NR | NR | OR 1.7 (95%CI 0.4 to 6.3) | NS |
| Deep vein thrombosis | Seitz 2014 | 47/8818 (0.5%) | 41/12155 (0.3%) | P=0.03 | NS when matched |
| Pulmonary Embolism   |         | 100/8818 (1.1%) | 93/12155 (0.8%) | P=0.006 | NS when matched |
| Study                     | Condition                          | Event          | Event Count | Event %  | Control Count | Control %  | p-value   | Odds Ratio | 95% CI     | Significance |
|--------------------------|------------------------------------|----------------|-------------|-----------|---------------|-------------|-----------|------------|------------|-------------|
| Sutcliffe 1994           | Deep vein thrombosis               | 16/950         | 16/950      | 1.7%      | 14/383        | 14/383      | P<0.05    | NS         |            |             |
|                         | Pulmonary Embolism                 | NR             | NR          | NS        |               |             |           |            |            |             |
| Bigler 1985              | Wound infection                    | 1/20           | 1/20        | NR        |               |             |           |            |            |             |
| Fields 2015              | Urinary Tract infection            | 5.76%          | 8.87%       | P<0.0001  |               |             |           |            |            |             |
|                         |                                    |                |             |           |               |             |           |            |            |             |
| Rashid 2013              | Urinary Tract infection            | NR             | NR          | NS        |               |             |           |            |            |             |
| Basques 2015             | Wound infection                    | 94/7253 (1.3%) | 39/2589 (1.5%) | NS      |               |             |           |            |            |             |
| Renal                    | Basques 2015                       | Acute Renal Failure | 29/7253 (0.4%) | 10/2589 (0.4%) | NS |               |             |           |            |            |             |
| Bigler 1985              | Urinary retention                  | 4/20           | 5/20        | NS        |               |             |           |            |            |             |
| Chu 2015                 | Acute Renal Failure                | 78/52043 (0.15%) | 56/52044 (0.11%) | P=0.06  |               |             |           |            |            |             |
| Naja 2000                | Acute Renal Failure                | 2/30 (6%)      | 0/30 (0%)   | NS        |               |             |           |            |            |             |
| Overall complications    | Gilbert 2000                       | Serious medical complications | 55/311 (17.7%) | 79/430 (18.4%) | OR 0.92 (95%CI 0.61 to 1.4) | NS |             |            |            |             |
|                         | Gilbert 2000                       | Fewer medical complications | 109/311 (35.1%) | 151/430 (35.1%) | OR 1.28 (95%CI 0.90 to 1.82) | NS |             |            |            |             |
|                         | Whiting 2015                       | Surgical complications | 15/311 (4.8%) | 19/430 (4.4%) | OR 1.08 (95%CI 0.65 to 1.21) | NS |             |            |            |             |
|                         | Major complications                | NR             | NR          | OR 1.43 (95%CI 1.16-1.77) | NS |             |            |            |             |             |
|                         | Minor complications                | NR             | NR          | OR 1.02 (95%CI 0.82 to 1.26) | NS |             |            |            |             |             |
|                         | All complications                  | NR             | NR          | OR 1.24 (95%CI 1.05 to 1.48) | NS |             |            |            |             |             |
| Study (Year) | Complication Type | Count 1 | Count 2 | Odds Ratio (95% CI) | p-value | p-value Qualification |
|-------------|-------------------|---------|---------|---------------------|---------|----------------------|
| Hekimoglu Sahin 2012 | All complications | 2357/4813 (48.97%) | 830/1815 (45.75%) | OR 1.29 (95%CI 1.13 to 1.47), p=0.0002 | Favours RA |
| Ilango 2015 | All complications | NR | NR | NS |
| Koval 1999 | All complications | 41/362 (11.3%) | 32/280 (11.4%) | NS |
| Le Liu 2014 | All complications | 17/72 (23.6%) | 50/145 (34.5%) | P=0.165 NS |
| Le Wendling 2012 | All complications | NR | NR | OR 1.7 (95%CI 0.7 to 4.1) NS |
| Radcliffe 2013 | All complications | 22% | 19% | Log regression model p=0.002 Favours RA |
| Shih 2010 | All complications | 21/167 (12.6%) | 9/168 (5.4%) | P<0.02 Favours RA |
| Chu 2015 | ITU admissions | 5743/52043 (11.03%) | 3205/52044 (6.16%) | OR 1.95 (95%CI 1.87 to 2.05), p<0.001 Favours RA |
| Chu 2015 | ITU stay >3 days | 1206/52043 (2.32%) | 411/5204 (0.79%) | P<0.001 Favours RA |
| Baumgarten 2012 | Pressure ulcers | 10/328 (3.0%) | 18/313 (5.8%) | OR 1.3 (95%CI 1.0-1.6) Favours GA |
| Casati 2003 | Hypotension requiring crystalloid infusion | 12/15 (80%) | 7/15 (46%) | P=0.05 NS |
| Study            | Outcome                        | Control | Treatment | P-value   | Conclusion   |
|------------------|--------------------------------|---------|-----------|-----------|--------------|
| Maia 2014        | Intraoperative hypotension     | 25/50   | 80/173    | P=0.014   | Favours RA   |
| Minville 2008    | Intraoperative hypotension     | 35/42   (83%) | 74/109 (68%) | NS         |
| Gadsden 2016     | Intraoperative hypotension     | 569/745 | 1144/1528 | P<0.0001  | Favours RA   |
| Messina 2013     | Haemodynamic changes first 10min | Mean arterial blood pressure, heart rate, systemic vascular resistance index changes. More disturbance in GA | Favours RA |
| Basques 2015     | Blood transfusion              | 2843/7253 (39.2%) | 851/2589 (32.9%) | Matched OR 1.34 (1.22 to 1.49), p<0.001 | Favours RA |
| Fields 2015      | Blood transfusion              | 45.49%  | 39.34%    | P<0.0001  | Favours RA   |
| Minville 2008    | Blood transfusion              | 23%     | 4%        | P<0.05    | Favours RA   |
| Shih 2010        | Blood loss                     | Median 250 (0-1600) ml | Median 200 (0-1200) ml | P=0.01    | Favours RA   |
| Chu 2015         | Stroke                         | 840/52043 (1.61%) | 717/52044 (1.38%) | OR 1.18 (95%CI 1.07 to 1.31), p=0.001 | Favours RA |
| Le Liu 2014      | Stroke                         | 5/72 (5.9%) | 4/145 (2.8%) | P=0.145 NS | NS           |

POMS is Post-operative morbidity survey
OR is odds ratio
NS is not significant; NR is not reported
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**Figure Legends**

**Figure 1**: PRISMA Flow Diagram. Legend: The PRIMSA diagram details our search and selection process applied during the review.

**Figure 2**: Forest plot of studies reporting the unadjusted relative risk of post-operative delirium with GA compared to spinal anaesthesia. Some studies are represented more than once to show results for different definitions of delirium, or for different assessment time-points. RR = relative risk, CI = confidence interval, MMSE = mini mental state examination, CAM = confusion assessment method, DSM-IV = Diagnostic and statistical manual of mental disorders 5, UCD = unspecified cognitive dysfunction.

**Figure 3**: Forest plot of studies reporting length of hospital stay. Weighted mean difference in number of days between GA and RA (GA minus RA). WMD > 0 means longer stay for GA and favours RA. WMD < 0 means longer stay for RA and favours GA. WMD = weighted mean difference, CI = confidence interval
Citations identified through other sources n=1

Citations identified by electronic searches n=4858

Excluded duplicate citations n=1495

Total citations left to screen n=3364

Citations excluded after screening of titles/abstracts n=3012

Articles retrieved for detailed evaluation n=352

Articles excluded n=248
- Study design n=90
- Could not locate n=11
- Duplicates n=29
- Incorrect population n=6
- No anaesthesia data n=32
- Outdated anaesthesia n=30
- Results not reported in relation to type of anaesthesia n=12
- Inappropriate comparison n=18
- Inappropriate outcome n=6

Studies included in systematic review n=104
| Study            | Assessment tool | Time-point          | RR (95% CI)  |
|------------------|-----------------|---------------------|--------------|
| RCT              | MMSE ≤ 2 point decline | Day 1 postop | 1.13 (0.60, 2.11) |
| Caeili 2003      | MMSE ≤ 2 point decline | Day 7 postop | 3.00 (0.35, 25.06) |
| Kamïn 2003       | CAM             | Day 0-1             | 0.68 (0.29, 1.60) |
| Kamïn 2003       | CAM             | Day 1-2             | 1.13 (0.35, 3.60) |
| Kamïn 2003       | CAM             | Day 2-3             | 1.81 (0.18, 18.35) |
| Kamïn 2003       | CAM             | Day 3-4             | 2.73 (0.12, 63.16) |
| Neuman 2016      | CAM             | Day 1-6 postop     | 0.00 (0.29, 66.40) |
| Parker & Griffiths 2015 | Unclear          | Unclear           | 0.14 (0.01, 2.64) |

| Prospective      | Assessment tool | Time-point          | RR (95% CI)  |
|------------------|-----------------|---------------------|--------------|
| Bitstch 2006     | MMSE ≤ 4 point decline | Day 2-7     | 1.23 (0.88, 1.72) |
| Bitstch 2006     | MMSE ≤ 20%      | Day 2-7             | 0.85 (0.22, 3.30) |
| Björk and Lund 2015 (SC) | OBS + DSM-IV | After 6 hours minimum postop | 1.57 (0.96, 2.50) |
| Björk and Lund 2015 (MPA) | OBS + DSM-IV | After 6 hours minimum postop | 0.70 (0.39, 1.30) |
| Gilbert 2009     | CAM             | Typically 5-10 days postop | 1.01 (0.80, 1.20) |
| Ilango 2016      | Clinical judgement + behaviours | Any time during postoperative recovery | 0.86 (0.70, 1.06) |
| Julliart 2009    | CAM             | Up to 5 days postop | 0.49 (0.14, 1.73) |
| Koval 1988       | Unclear         | Not specified       | 0.35 (0.12, 1.03) |

| Retrospective    | Assessment tool | Time-point          | RR (95% CI)  |
|------------------|-----------------|---------------------|--------------|
| Kim 2013         | DSM-IV          | Within 30 days      | 1.17 (0.72, 1.88) |
| Kontinen 2006    | Unclear         | Within 5 days postop | 0.88 (0.19, 4.00) |
| Luger 2014       | DSM-IV          | Not specified       | 1.47 (0.90, 3.32) |
| Luger 2014       | DSM-IV or UCC   | Not specified       | 1.30 (0.85, 1.97) |
| O'Hara 2000      | Unclear         | Within 7 days       | 0.73 (0.58, 0.70) |
| Shih 2010        | Unclear         | Before discharge    | 0.04 (0.03, 0.99) |

248x205mm (300 x 300 DPI)
### Table: Comparison of Anaesthesia Types

| Study       | Design | Anaesthesia Type | No. GA | No. RA | WMD (95% CI)         |
|-------------|--------|------------------|-------|-------|----------------------|
| RCT         | RCT    | Spinal           | 164   | 158   | -0.30 (-3.39, 2.79)  |
| Chu 2015    | Retrospective | Intravenous + Epidural | 52944 | 52944 | 0.33 (0.24, 0.42)    |
| Le-Henderson 2012 | Retrospective | Regional        | 236   | 71    | 0.19 (0.11, 0.27)    |
| Seitz 2014  | Retrospective | Regional        | 6136  | 6133  | 0.10 (-0.08, 0.06)   |
| Naja 2000   | Prospective | Combined Spinal/EPID | 3C    | 3C    | 6.90 (4.57, 9.23)    |
| Hekimoglu Sahn 2012 | Retrospective | Spinal & Epidural | 67   | 118   | -0.28 (-2.79, 2.23)  |
| Le Liu 2014 | Retrospective | Peripheral nerve block | 72 | 145 | 0.57 (0.10, 1.04)    |
| Rashid 2013 | Retrospective | Regional        | 107   | 87    | 0.72 (-1.18, 2.62)   |
| Sykora 1988 | Retrospective | Epidural        | 201   | 142   | 8.20 (5.21, 11.19)   |

**WMD >0 favours regional anaesthesia**

252x201mm (300 x 300 DPI)
Appendix A: Example of search strategy

exp Hip fracture/
hip fracture.mp.
(fracture$ adj2 (hip or femur$ or femor$)).tw.
or/1-3
exp an$esthesia/
an$esthesia.mp.
(anesthe$ or anaesthe$).tw.
an$ethetic.mp.
exp anesthetics/
exp general an$esthesia/
general an$esthesia.mp.
Anesthesia/ (43366)
exp Anesthesia, General/
general an$esthesia.mp.
sedation.mp. (28516)
exp regional an$esthesia/
regional an$esthesia.mp.
peripheral an$esthesia.mp.
central blockade.mp.
central block.mp.
spinal an$esthesia/
spinal an$esthesia.mp.
epidural an$esthesia/
epidural an$esthesia.mp.
local an$esthesia.mp.
infiltrative an$esthesia.mp.
peripheral nerve block.mp.
intravenous regional an$esthesia.mp.
systemic local an$esthesia.mp.
nerve block$/
nerve block$.mp.
neuroaxial blockade.mp.
Anesthesia/ or exp Anesthesia, Intravenous/
exp inhalation an$esthesia/
inhalation an$esthesia.mp.
or/5-36
4 and 37
### Appendix B: Table of eligible on-going studies

| Title                                                                 | ID          | Comparison                                      | Status                     | Design                                      | Contact        | Country   |
|---------------------------------------------------------------------|-------------|-------------------------------------------------|----------------------------|---------------------------------------------|----------------|-----------|
| Comparison of Combined Lumbar and Sacral Plexus Block With Sedation Versus General Endotracheal Anesthesia on Postoperative Outcomes in Elderly Patients Undergoing Hip Fracture Surgery (CLSB-HIPELD): Rationale and Design of a Prospective, Multicenter, Randomized Controlled Trial | NCT03318133 | General vs Combined lumbar plexus and sacral plexus block (CLSB) | Not yet recruiting patients | Double blind randomised trial | Xiaofeng Wang | China     |
| The Comparative Effects of Regional or General Anesthesia on the Prognosis of Hip | NCT03116490 | General vs Regional                              | Recruiting patients        | Prospective observational cohort            | Ting Li        | China     |
| Fracture Surgery on Elderly Patients | Variations in Anaesthesia care for hip fracture surgery | NCT02787031 | General vs Neuraxial | Recruitment completed but no results available | Retrospective observational cohort | Ottawa Hospital Research Institute | Canada |
|------------------------------------|------------------------------------------------------|--------------|----------------------|-----------------------------------------------|---------------------------------|-----------------------------------|--------|
| Regional versus general anaesthesia for promoting independence after hip fracture | NCT02507505 | General vs Regional | Recruiting patients | Double blind randomised trial | Mark Powell/Mark Neuman | USA |
| Effect of anaesthesia on post-operative delirium in elderly patients undergoing hip fracture surgery | NCT02213380 | General vs Regional | Recruiting patients | Open label randomised controlled trial | Ting Li/Sishi Chen | China |
| The safety of anaesthesia management for traumatic hip surgery in elderly | NCT02692989 | General vs Regional | Ongoing, but not recruiting patients | Retrospective observational cohort | Subhi M Alghanem | Jordan |
| Anaesthesia and post-operative mortality after proximal femur fractures | NCT02406300 | Peripheral nerve block/General vs Subarachnoid anaesthesia | Enrolling patients by invite only | Double blind randomised controlled trial | Raul Carvalho | Portugal |
| Study Title                                                                 | NCT Number  | Comparison                        | Design                               | Outcomes                              | Principal Investigator | Country        |
|---------------------------------------------------------------------------|-------------|-----------------------------------|--------------------------------------|---------------------------------------|------------------------|----------------|
| Effect of anaesthesia in fracture healing                                 | NCT02621255| General vs Regional               | Recruiting patients                  | Double blind randomised trial         | Ebru Biricik           | Turkey         |
| Mortality following surgery for proximal femoral fractures                | NCT01807039| General vs. Subarachnoid anaesthesia | Study has been completed             | Retrospective observational cohort    | Petr Štourač           | Czech Republic |
| ICTRP                                                                     |             |                                   |                                      |                                       |                        |                |
| Hypobaric Lateral Spinal Anesthesia Versus General Anesthesia: Hemodynamic Stability and Short Term Cardiovascular Complications in Elderly Patients Undergoing Hip Fracture Surgery. | NCTNCT03373864| General vs Hypobaric lateral spinal | Recruiting patients                  | Randomised controlled trial   | Claire Delsuc | France         |
| Effects of different anesthesia methods on postoperative complications and hospital mortality in elderly patients | ChiCTR-RRC-17013545 | General vs Regional               | Recruiting patients                  | Prospective cohort                   | Xu Mao                | China          |
| with hip fracture | IRCT201308316280N4 | General vs Spinal | Completed | Double blind randomised trial | Mohammad Haghighi | Iran |
|-------------------|--------------------|------------------|-----------|-------------------------------|--------------------|------|
| **ISRCTN**        |                    |                  |           |                               |                    |      |
| A Feasibility     | ISRCTN15165914     | General vs Regional | Recruiting patients | Randomised controlled trial | Joyce Yeung | UK  |
| Randomised        |                    |                  |           |                               |                    |      |
| Controlled Trial  |                    |                  |           |                               |                    |      |
| to compare Regional versus General Anaesthesia in Reducing Delirium in patients with Hip Fractures | | | | | | |
## PRISMA 2009 Checklist

| Section/topic               | # | Checklist item                                                                 | Reported on page # |
|-----------------------------|---|--------------------------------------------------------------------------------|-------------------|
| **TITLE**                   |   |                                                                                |                   |
| Title                       | 1 | Identify the report as a systematic review, meta-analysis, or both.             |                   |
| **ABSTRACT**                |   |                                                                                |                   |
| Structured summary          | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2,3               |
| **INTRODUCTION**            |   |                                                                                |                   |
| Rationale                   | 3 | Describe the rationale for the review in the context of what is already known.  | 5,6               |
| Objectives                  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6                 |
| **METHODS**                 |   |                                                                                |                   |
| Protocol and registration   | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 6                 |
| Eligibility criteria        | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 6                 |
| Information sources         | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 6                 |
| Search                      | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Appendix A        |
| Study selection             | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 7                 |
| Data collection process     | 10| Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 7                 |
| Data items                  | 11| List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 8                 |
| Risk of bias in individual studies | 12| Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 23-27             |
| Summary measures            | 13| State the principal summary measures (e.g., risk ratio, difference in means).     | 8                 |
| Synthesis of results        | 14| Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis. | 8                 |
## PRISMA 2009 Checklist

| Section/topic                        | # | Checklist item                                                                                                                                  | Reported on page # |
|-------------------------------------|---|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Risk of bias across studies         | 15| Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).         | 23-27             |
| Additional analyses                 | 16| Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.       | NA                |

### RESULTS

| Study selection                     | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 8, Figure 1       |
| Study characteristics                | 18| For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.             | 18-22             |
| Risk of bias within studies         | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                          | 23-27             |
| Results of individual studies       | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Table 2a/b,3,4, Figure 2,3 |
| Synthesis of results                | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                        | NA                |
| Risk of bias across studies         | 22| Present results of any assessment of risk of bias across studies (see Item 15).                                                                 | 23-27             |
| Additional analysis                 | 23| Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                              | NA                |

### DISCUSSION

| Summary of evidence                 | 24| Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 13,14             |
| Limitations                         | 25| Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 15, 16            |
| Conclusions                         | 26| Provide a general interpretation of the results in the context of other evidence, and implications for future research.                         | 16                |

### FUNDING

| Funding                             | 27| Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.          | 16                |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org)