The efficacy of peri-operative interventions to decrease postoperative delirium in non-cardiac surgery: a systematic review and meta-analysis.

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Summary
The purpose of this meta-analysis was to determine the efficacy of peri-operative interventions in decreasing the incidence of postoperative delirium. An electronic search of four databases was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to. We included randomised controlled trials of non-cardiac surgery with a peri-operative intervention and that reported postoperative delirium, and identified 29 trials. Meta-analysis revealed that peri-operative geriatric consultation (OR 0.46, 95% CI 0.32–0.67) and lighter anaesthesia (OR 2.66, 95% CI 1.27–5.56) were associated with a decreased incidence of postoperative delirium. For the other interventions, the point estimate suggested possible protection with prophylactic haloperidol (OR 0.62, 95% CI 0.36–1.05), bright light therapy (OR 0.20, 95% CI 0.03–1.19) and general as opposed to regional anaesthesia (OR 0.76, 95% CI 0.47–1.23). This meta-analysis has shown that peri-operative geriatric consultations with multicomponent interventions and lighter anaesthesia are potentially effective in decreasing the incidence of postoperative delirium.

Introduction
As the global population ages, so the number of elderly patients with more co-morbidities requiring surgical interventions and procedures is increasing [1, 2]. These patients represent a significant proportion of the estimated annual 200 million surgical procedures conducted globally [3].

Postoperative delirium is associated with serious postoperative complications [2], which decrease functional capacity, prolong recovery and discharge, and directly increase healthcare costs [2, 4–8]. Patients suffering delirium have increased numbers of surgical complications, including fractures, urinary and respiratory tract infections, and vascular events [8]. Delirium also increases long-term morbidity through delayed functional and cognitive recovery [9], subsequent institutionalisation [5, 6] and postoperative depression [4].

Outcomes could be improved by systematic identification of important risk factors for delirium and identification of preventative measures that decrease the incidence of delirium and the subsequent
associated morbidity [10]. The purpose of this systematic review and meta-analysis was to determine the efficacy of pharmacological and non-pharmacological peri-operative interventions to decrease delirium.

Methods
Using the PICOT (patient/intervention/comparison/outcome/time) question structure [11], we posed the following research question: ‘Which peri-operative interventions during non-cardiac surgery have been independently associated with a reduction in delirium within the first seven postoperative days?’ The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines were followed [12]. Trials were considered eligible if they tested a peri-operative intervention aimed at reducing delirium after non-cardiac surgery in a randomised controlled manner. The primary outcome was the incidence of delirium within seven days of surgery. Eligible trials had to diagnose delirium using a test recommended by the Diagnostic and Statistical Manual of Mental Disorders (DSM): DSM-III; DSM-III-R; DSM IV [13]; or by the International Classification of Diseases, 10th edition [14]. We also included trials that used pre-operative and postoperative mini-mental state examinations in the diagnosis of delirium.

We searched four databases: Ovid Healthstar 1966 to Jan 2012; Ovid Medline 1946 to March 2012; EMBASE 1974 to August 2012; and the Cochrane Library to March 2012. The search terms included: (delirium).mp; (cognitive disorder).mp; and (surgery).mp. Exclusions were (cardiac surgery or coronary artery bypass or CABG).mp. The search was limited to English language, human and adult. All reviews, letters, case reports, comment, editorials and guidelines were removed, as were duplicate publications (Appendix 1). A manual search of the reference lists of all included papers was also conducted for further eligible studies. Concordance of article extraction was determined using a kappa statistic. Using a standardised data extraction sheet, we extracted data on: the outcome of delirium following a peri-operative intervention; the specific intervention tested; patient age; type of surgery; and the use of premedication. The quality of each study was assessed using the Jadad score (Appendix 2) [15].

Meta-analysis was conducted using Review Manager Version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011). Heterogeneity between studies was assessed using univariate chi-squared analysis. Random or fixed effects models were used based on the presence or absence of significant heterogeneity between studies, respectively. Pooled dichotomous outcomes were reported as odds ratios (OR) with 95% CI. Where an intervention was associated with benefit, a funnel plot was constructed to determine if the outcomes reported were affected by publication bias. For interventions that were not significantly associated with a decrease in delirium, a power analysis was conducted to determine if the sample size was adequately powered for the outcome. The power analysis was based on the incidence in the control group, with an expected 25% relative risk reduction for an efficacious intervention.

Results
We identified 1376 studies from our literature search, of which 56 studies were selected for full paper analysis; the kappa statistic was 83%. From these studies, 29 were finally included in our meta-analysis (Fig. 1). Nineteen of the studies were of a high quality with a Jadad score of 4 or 5 [16–34], and 10 were low-quality studies with a Jadad score < 4 (Table 1) [35–44].

The following interventions to decrease delirium were tested in more than one trial and a meta-analysis was therefore possible (Figs. 2–9): geriatric (or multicomponent) consultation vs standard care, where peri-operative geriatric consultation constituted a proactive, comprehensive geriatric assessment along with management and rehabilitation to decrease the outcome of delirium [36, 38, 40]; deep vs light anaesthesia [19, 20, 32]; intravenous vs inhalational anaesthesia [18, 29]; general vs regional anaesthesia [30, 34, 43]; haloperidol vs placebo [21, 33, 37]; donepezil (a cholinesterase inhibitor) vs placebo [26, 27, 31]; gabapentin vs placebo [16, 25]; and bright light therapy vs standard care [41, 42]. Bright light therapy was instituted after extubation of the trachea and study patients received two hours of bright light therapy daily.

Only two interventions were associated with significantly decreased delirium: peri-operative geriatric consultation (Fig. 2) and light as opposed to deep
anaesthesia (Fig. 3). There was no significant heterogeneity for these two interventions. The funnel plot suggested that there was no publication bias associated with peri-operative geriatric consultations and delirium. However, there may have been publication bias with deep vs light anaesthesia (Fig. 10). The peri-operative geriatric consultation studies were of poorer quality (Jadad scores ≤ 3), largely due to inadequacies in randomisation and/or blinding. Depth of anaesthesia studies were good quality studies, (Jadad scores > 3). For the other interventions, the point estimate suggested possible protection with the use of prophylactic haloperidol, bright light therapy and general as opposed to regional anaesthesia. The power analyses showed that the sample size was inadequate for all the interventions included in the meta-analysis, with the exception of the peri-operative geriatric consultation.

Interventions that were reported in single trials included: pharmacological sleep–wake rhythm control vs control (p = 0.023) [35]; intrathecal morphine vs patient controlled morphine (no significant difference) [17]; continuation of antidepressant therapy vs control (p = 0.05) [22]; nitrous oxide vs oxygen (p = 0.78) [24]; patient-controlled epidural analgesia vs patient-controlled analgesia (p < 0.05) [39]; fascia iliac compartment block vs control (OR 0.45, 95% CI 0.23–0.87) [28]; and desflurane vs sevoflurane (no significant difference) [44].

Discussion
The main findings of this meta-analysis are that peri-operative geriatric consultations, which included multi-component interventions, and lighter as opposed to deeper anaesthesia were effective in decreasing post-operative delirium. The point estimate for peri-operative geriatric consultation was robust without heterogeneity, yet these clinical trials are at a high risk of bias due to inadequate randomisation and/or blinding. The point estimate for deep vs light anaesthesia showed significant heterogeneity, and there may be publication bias associated with this intervention.

Postoperative delirium occurs commonly among geriatric patients after both non-cardiac and cardiac surgery, with a reported incidence as high as 73% [2, 4]. It is characterised by acute cognitive decline after surgery associated with altered perception, attention and inappropriate behaviour [5, 6]. There are two standard definitions used for delirium: an acute and fluctuating disturbance of consciousness with signs of inattention, accompanied by a change in cognition and perception [13]; or an aetiologically non-specific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking and memory, including disturbances of emotion, psychomotor and the sleep–wake cycle [14]. Delirium is usually apparent on the first or second day postoperatively and symptoms usually worsen at night [7].

Delirium is a common complication following hip fracture surgery and the three trials of peri-operative geriatric consultations were conducted in this population. Multi-component and systemic assessment addressed urinary tract infections, hypoxia, anaemia, constipation, sleep disorders and nutritional deficiencies, which may all have a role in the aetiology and duration of delirium [38]. This meta-analysis lends support to multidisciplinary peri-operative medicine interventions to decrease delirium.
Table 1  Characteristics of included studies with peri-operative interventions to decrease postoperative delirium. Values are mean (SD) or number.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Assessment of POD</th>
<th>Timing of evaluation</th>
<th>Age: years</th>
<th>Type of surgery</th>
<th>Type of anaesthesia</th>
<th>Premedication</th>
<th>Jadad score [15]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aizawa et al. [35], 2002</td>
<td>Control of sleep-wake rhythm vs control</td>
<td>DSM IV</td>
<td>Day 1–6</td>
<td>76 (5)</td>
<td>Abdominal</td>
<td>GA + epidural</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Akarsu et al. [16], 2012</td>
<td>Pregabalin vs control</td>
<td>MMSE</td>
<td>Day 1–10</td>
<td>44–68</td>
<td>Abdominal</td>
<td>GA: TIVA</td>
<td>Nil</td>
<td>4</td>
</tr>
<tr>
<td>Beaussier et al. [17], 2006</td>
<td>Intrathecal morphine vs IV PCA morphine</td>
<td>CAM</td>
<td>Day 1</td>
<td>78 (5)</td>
<td>Abdominal</td>
<td>GA</td>
<td>Hydroxyzine 1 mg.kg⁻¹</td>
<td>5</td>
</tr>
<tr>
<td>Cai et al. [18], 2012</td>
<td>IV vs inhalational</td>
<td>MMSE ≤ 25</td>
<td>Day 1, 3, 5, 8, 15</td>
<td>70.1 (4.6)</td>
<td>Non-cardiovascular</td>
<td>GA</td>
<td>Diazepam 10 mg, atropine 0.5 mg</td>
<td>4</td>
</tr>
<tr>
<td>Chan et al. [19], 2013</td>
<td>BIS guided vs routine care</td>
<td>DSM III</td>
<td>Day 1</td>
<td>68.1 (8.2)</td>
<td>Non-cardiovascular</td>
<td>GA</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Deschodt et al. [36], 2012</td>
<td>IGCT vs standard care</td>
<td>CAM</td>
<td>Day 1–3</td>
<td>80.4 (7)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Jildenstal et al. [20], 2011</td>
<td>AEP vs control</td>
<td>MMSE &lt; 25</td>
<td>Day 1–3</td>
<td>18–92</td>
<td>Ophthalmic</td>
<td>GA</td>
<td>Midazolam, paracetamol 1 g</td>
<td>4</td>
</tr>
<tr>
<td>Kalisvaart et al. [21], 2005</td>
<td>Haloperidol vs placebo</td>
<td>DSM IV, CAM, DRS</td>
<td>Day 1–3</td>
<td>78.7 (0.64)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Kaneko et al. [37], 1999</td>
<td>Haloperidol vs placebo</td>
<td>DSM IIIR</td>
<td>Day 1–8</td>
<td>72.4 (8.2)</td>
<td>Abdominal</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Kudoh et al. [22], 2002</td>
<td>Antidepressant continued vs stopped</td>
<td>CAM</td>
<td>Day 1–2</td>
<td>49.5 (9.4)</td>
<td>Non-cardiovascular</td>
<td>GA</td>
<td>NR</td>
<td>4</td>
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<tr>
<td>Larsen et al. [23], 2010</td>
<td>Olanzapine vs placebo</td>
<td>DSM IIIR, CAM</td>
<td>Day 1–3</td>
<td>72.4 (6.1)</td>
<td>Orthopaedic</td>
<td>GA or regional</td>
<td>Midazolam 1–2 mg, fentanyl</td>
<td>5</td>
</tr>
<tr>
<td>Leung et al. [24], 2006</td>
<td>N₂O vs O₂</td>
<td>DSM IIIR, CAM</td>
<td>NR</td>
<td>(65–95)</td>
<td>Non-cardiovascular</td>
<td>GA</td>
<td>Fentanyl 2 μg.kg⁻¹</td>
<td>4</td>
</tr>
<tr>
<td>Leung et al. [25] 2006</td>
<td>Gabapentin vs placebo</td>
<td>DSM IIIR, CAM</td>
<td>Day 1–3</td>
<td>57.2 (10.3)</td>
<td>Spinal</td>
<td>GA</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Assessment of POD</td>
<td>Timing of evaluation</td>
<td>Age; years</td>
<td>Type of surgery</td>
<td>Type of anaesthesia</td>
<td>Premedication</td>
<td>Jadad score</td>
</tr>
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<td>---------------------------</td>
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<tr>
<td>Liptzin et al. [26], 2005</td>
<td>Donepezil vs placebo</td>
<td>DSM IV, CAM</td>
<td>Day 1–5</td>
<td>67.2 (8.7)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Lundstrom et al. [38], 2007</td>
<td>Intervention geriatric programme vs conventional care</td>
<td>DSM IV</td>
<td>Day 1</td>
<td>I: 82.3 (6.6) C: 82 (5.6)</td>
<td>Orthopaedic</td>
<td>Regional/GA</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Mann et al. [39], 2000</td>
<td>PCA vs PCEA</td>
<td>DSM III</td>
<td>Day 1–7</td>
<td>I: 76.8 (4.7) C: 76.1 (5.6)</td>
<td>Abdominal</td>
<td>GA</td>
<td>Hydroxyzine 100 mg</td>
<td>3</td>
</tr>
<tr>
<td>Marcantonio et al. [40], 2001</td>
<td>Geriatric consultation vs usual</td>
<td>CAM</td>
<td>Day 1</td>
<td>I: 78 (8) C: 80 (8)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Marcantonio et al. [27], 2011</td>
<td>Donepezil vs placebo</td>
<td>CAM</td>
<td>Day 1–3</td>
<td>I: 88 (5.2) C: 87 (3.7)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Mouzopoulos et al. [28], 2009</td>
<td>Fascia iliaca compartment block vs placebo</td>
<td>DSM IV, CAM</td>
<td>Day 1–6</td>
<td>I: 72 (4) C: 73 (4)</td>
<td>Orthopaedic</td>
<td>Epidural</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Nishikawa et al. [29], 2004</td>
<td>Propofol vs sevoflurane</td>
<td>DRS, DSM III</td>
<td>Day 1–3</td>
<td>I: 71 (8) C: 71 (7)</td>
<td>Abdominal</td>
<td>GA/epidural</td>
<td>nil</td>
<td>4</td>
</tr>
<tr>
<td>Ono et al. [41], 2011</td>
<td>Bright light vs control</td>
<td>NEECHAM, DSM IV-TR</td>
<td>Day 1–3</td>
<td>I:63.4 (9.7) C:63.8 (7.8)</td>
<td>Thoracic</td>
<td>GA</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Papaioanno et al. [30], 2005</td>
<td>GA vs regional</td>
<td>DSM III</td>
<td>Day 2,3</td>
<td>&gt; 60</td>
<td>Orthopaedic, urology, vascular</td>
<td>NR</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sampson et al. [31], 2007</td>
<td>Donepezil vs placebo</td>
<td>DSM IV</td>
<td>Day 1–5</td>
<td>52–86 (67.8)</td>
<td>Orthopaedic</td>
<td>NR</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Sieber et al. [32], 2010</td>
<td>Deep vs light sedation</td>
<td>CAM</td>
<td>Day 1–3</td>
<td>I: 81.8 (6.7) C: 81.2 (7.6)</td>
<td>Orthopaedic</td>
<td>Spinal</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Slor et al. [34], 2011</td>
<td>GA vs regional</td>
<td>DSM IV, CAM</td>
<td>Day 1–7</td>
<td>I:76.7 (5.5) C:78.2 (6.8)</td>
<td>Non-cardiovascular</td>
<td>GA and regional</td>
<td>NR</td>
<td>5</td>
</tr>
<tr>
<td>Taguchi et al. [42], 2007</td>
<td>Bright light vs control</td>
<td>NEECHAM</td>
<td>Day 1–7</td>
<td>29–71</td>
<td>Thoracic</td>
<td>GA</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>
Delirium is multifactorial, and anaesthetic techniques is another potentially modifiable risk factor [12, 13]. Intra-operative monitoring of depth of anaesthesia using bispectral index (BIS) or auditory evoked potentials has shown to facilitate titration of anaesthetic drugs. Bispectral index values between 40 and 60 during anaesthesia have been associated with decreased awareness, earlier recovery profiles and faster emergence [19]. Chan et al. demonstrated that titrating anaesthetic agents to maintain BIS between 40 and 60 and avoiding episodes of deep anaesthesia (BIS \(< 40\)) reduced the risk of delirium (p = 0.01) [19]. Sieber et al. found that light sedation (BIS \(> 80\)) during spinal anaesthesia for orthopaedic surgery decreased the occurrence of delirium by 50% when compared with deep sedation (BIS \(~50\)) (p = 0.02) [32]. Depth of anaesthesia guided by auditory evoked potentials demonstrated that patients with lighter anaesthesia sustained fewer intra-operative events, had higher blood pressure, required less fluids or vasopressors, and were at a lower risk of developing early postoperative decline [20].

Regarding the intra-operative measures that were identified, neither intravenous vs inhalational anaesthesia, nor regional vs general anaesthesia, showed any effect on postoperative delirium. Although both of these analyses were underpowered, the point estimates favoured inhalational and general anaesthesia. In contrast, another meta-analysis of the efficacy of general and regional anaesthesia failed to show a significant difference (five studies), and suggested that general anaesthesia may increase the risk of developing postoperative cognitive dysfunction [45].

Our meta-analysis has found a trend to protection with the use of haloperidol. The dose of haloperidol varied between the studies. Wang et al. used 0.5 mg haloperidol as an intravenous bolus postoperatively, followed by an infusion at 0.1 mg.h\(^{-1}\) for 12 h; Kaneko et al. administered 5 mg haloperidol intravenously per day for five days, and Kalisvaart et al. used oral haloperidol 1.5 mg pre-operatively and for three days postoperatively [21, 33, 37]. A recent meta-analysis conducted by Teslyar et al. looked at antipsychotics as a group (haloperidol, olanzapine and risperidone) and they also showed a trend to a reduction in delirium with the peri-operative use of antipsychotics [46].

### Table 1. (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Age; years</th>
<th>Type of surgery</th>
<th>Type of anaesthesia</th>
<th>Premedication</th>
<th>Jadad score</th>
<th>Timing of evaluation</th>
<th>Assessment of POD</th>
<th>Type of anaesthesia</th>
<th>Premedication</th>
<th>Type of surgery</th>
<th>Timing of evaluation</th>
<th>Assessment of POD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al. [33] 2012</td>
<td>Haloperidol vs placebo</td>
<td>I: 74 (5.8)</td>
<td>Non-cardiovascular</td>
<td>GA/regional, GA and regional</td>
<td>NR</td>
<td>5</td>
<td>Day 1</td>
<td>CAM</td>
<td>I:74 (5.8)</td>
<td>C: 74.4 (7.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Berggren et al. [43] 1987</td>
<td>GA vs regional</td>
<td>I:77 (7)</td>
<td>Orthopaedics</td>
<td>GA and regional</td>
<td>Pethidine, 25-50 mg</td>
<td>3</td>
<td>Day 1</td>
<td>DSM III</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chen et al. [44], 2001</td>
<td>Desflurane vs sevoflurane</td>
<td>I: 75 (8)</td>
<td>Orthopaedics</td>
<td>GA</td>
<td>Midazolam 1 mg</td>
<td>3</td>
<td>Day 1</td>
<td>MMSE</td>
<td></td>
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</tbody>
</table>

POD, postoperative delirium; DSM, Diagnostic and Statistical Manual of Mental Disorders; I, intervention; C, control; GA, general anaesthesia; NR, not reported; MMSE, Mini-mental state exam; TIVA, total intravenous anaesthesia; CAM, confusion assessment method; IV, intravenous; PCA, patient-controlled analgesia; BIS, bispectral index; IGCT, inpatient geriatric consultation team; AEP, auditory evoked potential; DRS, delirium rating scale; PCEA, patient-controlled epidural analgesia; NECHAM, Neelon and Champagne confusion scale.
Figure 2 Meta-analysis of the efficacy of peri-operative geriatric consultation vs standard care on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 3 Meta-analysis of the efficacy of depth of anaesthesia vs standard care on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 4 Meta-analysis of the efficacy of intravenous vs inhalational anaesthesia on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 5 Meta-analysis of the efficacy of general vs regional anaesthesia on outcome of postoperative delirium. M-H, Mantel-Haenszel.
Figure 6 Meta-analysis of the efficacy of haloperidol on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 7 Meta-analysis of the efficacy of donepezil on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 8 Meta-analysis of the efficacy of peri-operative gabapentin on outcome of postoperative delirium. M-H, Mantel-Haenszel.

Figure 9 Meta-analysis of the efficacy of bright light therapy on outcome of postoperative delirium. M-H, Mantel-Haenszel.
Gabapentin and pregabalin are γ-aminobutyric acid analogues that were developed as anticonvulsants, and recent evidence supports their use for chronic pain. In the postoperative period, they reduce pain and decrease opioid consumption. A pilot study by Leung et al. found that postoperative use of gabapentin decreased the incidence of delirium, and concluded that this was probably secondary to an opioid sparing effect [16, 25].

There is a close relationship between sleep disorders and the development of delirium [35]. Our meta-analysis found a trend to improved outcome in patients maintaining a sleep–wake cycle using bright light therapy. However, this intervention was also underpowered.

Due to the multifactorial nature of delirium, we are most likely to realise benefit when multiple interventions are instituted. This meta-analysis supports this approach where peri-operative geriatric consultations have been shown to be a potentially very powerful intervention to decrease delirium. We recommend that future interventional trials for delirium should consider a multi-component approach to preventing delirium.

There are a number of limitations to this meta-analysis. Firstly, of all the possible interventions investigated to decrease delirium, only peri-operative geriatric consultation and light vs deep anaesthesia were adequately powered. It is therefore possible that certain of the other interventions are efficacious; however, further research would be required to confirm this. Secondly, peri-operative geriatric consultation studies were limited to orthopaedic surgery. This research needs to be extended to other non-cardiac surgeries. Furthermore, the nature of multi-component consultations makes it difficult to exclude a strong bias due to poor randomisation and blinding, which is evident in this meta-analysis. In the pharmacological intervention studies, there was no standardisation of the anaesthetic technique. This is an important limitation, as this meta-analysis suggested that depth of anaesthesia may be an important determinant of delirium. Furthermore, there was no standardisation of the dosage of the pharmacological intervention between the trials analysed and this may be an important confounder in some studies. We also excluded foreign language studies, which could have impacted on the results of the meta-analysis. Finally, few studies assessed pre-operative risk for delirium, with no standardisation in timing of postoperative testing either. A standardised protocol for pre-operative risk assessment and outcome determination would be desirable in future studies.

In conclusion, the main findings of this meta-analysis are that peri-operative geriatric consultations that involve multi-component interventions, and lighter anaesthesia, are potentially effective in decreasing the outcome of delirium.

Competing interests
No external funding and no competing interests declared.

References
Anaesthesia 2013


Appendix 1

Search strategy

<table>
<thead>
<tr>
<th>Search</th>
<th>Terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>delirium.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
<tr>
<td>2</td>
<td>cognitive disorder.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
<tr>
<td>3</td>
<td>1 or 2</td>
</tr>
<tr>
<td>4</td>
<td>surgery.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
<tr>
<td>5</td>
<td>3 and 4</td>
</tr>
<tr>
<td>6</td>
<td>remove duplicates from 5</td>
</tr>
<tr>
<td>7</td>
<td>limit 6 to humans</td>
</tr>
<tr>
<td>8</td>
<td>limit 7 to “all adult (19 plus years)”</td>
</tr>
<tr>
<td>9</td>
<td>8 not “review”.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
<tr>
<td>10</td>
<td>9 not “All Child”.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
<tr>
<td>11</td>
<td>9 not “pediatric”.mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, an, ui]</td>
</tr>
</tbody>
</table>

Appendix 2

Jadad score used to measure the likelihood of bias of studies included in the meta-analysis [15]

| Category          | Criteria                                                        | Score: |
|-------------------|                                                                |        |
|                   |                                                                | Yes = 1 |
| Randomisation     | Is study described as randomised?                              |        |
|                   | Is randomisation appropriate?                                  |        |
| Blinding          | Is the study described as double blind?                        |        |
|                   | Is blinding appropriate/single blind?                          |        |
| Withdrawals/dropouts | Is there a description of withdrawal or dropouts?              |        |

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