Risk factors for delirium in adult patients receiving specialist palliative care: A systematic review and meta-analysis

Imogen Featherstone1, Trevor Sheldon2, Miriam Johnson3, Rebecca Woodhouse1, Jason W Boland3, Annmarie Hosie4, Peter Lawlor5,6, Gregor Russell7, Shirley Bush5,6 and Najma Siddiqi1

Abstract

Background: Delirium is common and distressing for patients receiving palliative care. Interventions targeting modifiable risk factors in other settings have been shown to prevent delirium. Research on delirium risk factors in palliative care can inform context-specific risk-reduction interventions.

Aim: To investigate risk factors for the development of delirium in adult patients receiving specialist palliative care.

Design: Systematic review and meta-analysis (PROSPERO CRD42019157168).

Data sources: CINAHL, Cochrane Database of Systematic Reviews, Embase, MEDLINE and PsycINFO (1980-2021) were searched for studies reporting the association of risk factors with delirium incidence/prevalence for patients receiving specialist palliative care. Study risk of bias and certainty of evidence for each risk factor were assessed.

Results: Of 28 included studies, 16 conducted only univariate analysis, 12 conducted multivariate analysis. The evidence for delirium risk factors was limited with low to very low certainty.

Potentially modifiable risk factors: Opioids and lower performance status were positively associated with delirium, with some evidence also for dehydration, hypoxaemia, sleep disturbance, liver dysfunction and infection. Mixed, or very limited, evidence was found for some factors targeted in multicomponent prevention interventions: sensory impairments, mobility, catheter use, polypharmacy (single study), pain, constipation, nutrition (mixed evidence).

Non-modifiable risk factors: Older age, male sex, primary brain cancer or brain metastases and lung cancer were positively associated with delirium.

Conclusions: Findings may usefully inform interventions to reduce delirium risk but more high quality prospective cohort studies are required to enable greater certainty about associations of different risk factors with delirium during specialist palliative care.

Keywords
Risk factors, delirium, palliative care, systematic review, meta-analysis

What is already known about the topic?
- Delirium is common and distressing in patients receiving palliative care.
- Studies of multicomponent interventions targeting modifiable delirium risk factors have reported delirium risk reduction in other settings.
- There is uncertainty about which delirium risk factors to address in patients receiving palliative care.

1Department of Health Sciences, University of York, York, UK
2Wolfson Institute of Population Health, Bart's and The London School of Medicine and Dentistry, Queen Mary University, London, UK
3Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull, Hull, England, UK
4School of Nursing, The University of Notre Dame Australia, Sydney, NSW, Australia
5Department of Medicine, Division of Palliative Care, University of Ottawa, Ottawa, ON, Canada
6Bruyere Research Institute, Ottawa, ON, Canada
7Bradford District Care NHS Foundation Trust, Saltaire, England, UK

Corresponding author:
Imogen Featherstone, Area 4, Department of Health Sciences, ARRC Building, University of York, York, England YO10 5DD, UK.
Email: imogen.featherstone@york.ac.uk
Introduction

Delirium is a distressing condition that is common in patients with advanced illness and associated with serious adverse outcomes. It is a manifestation of underlying and multifactorial pathophysiological abnormalities and is characterised by acute and fluctuating disturbances in attention, awareness and cognition. Multicomponent interventions targeting modifiable risk factors reduce the risk of delirium by around one in three cases during hospitalisation.

Systematic reviews suggest that although many risk factors for delirium are common across different patient populations and settings, their types and strengths of association vary. Reviews in older hospitalised patients and Intensive Care Units both found strong associations with older age, dementia and illness severity, but other significant risk factors differed and some were setting-specific, such as mechanical ventilation in intensive care. Vasilevskis et al. and Ahmed et al. have highlighted this variability between clinical settings and patient populations. Therefore, it is important to identify specific delirium risk factors, and the strengths of their association, for patients receiving palliative care. For example, palliative care patients’ risk of delirium may be increased due to factors related to advanced disease and multi-organ dysfunction and their frequent exposure to iatrogenic risk factors such as opioids. However, to our knowledge, no systematic review of delirium risk factors in patients receiving palliative care has yet been reported.

Synthesis of evidence on potentially modifiable risk factors is important to inform the design of interventions to reduce the risk of developing delirium. The term, ‘potentially modifiable’ is used in this review as the modifiability of some delirium risk factors in the palliative care context may vary, depending on factors such as the patients’ illness trajectory and goals of care. This evidence may also be used, in conjunction with that on non-modifiable risk factors, to develop predictive models of patient groups most likely to develop delirium.
compare occurrence of delirium in those exposed and not exposed to the potential risk factor.

Study designs eligible for inclusion included prospective and retrospective cohort studies, case-control, cross-sectional studies and randomised controlled trials. Case studies, case series, qualitative studies, opinion pieces and reviews were excluded. Studies published from 1980 onwards were included (when delirium was first included in DSM-III).17 No language restrictions were imposed. Abstracts were excluded if no full text was available.

**Study retrieval and selection**

The following databases were searched: CINAHL, Cochrane Database of Systematic Reviews (CDSR), Embase, MEDLINE and PsycINFO. The search strategy was developed with a Health Sciences Information Specialist. Key terms were: ‘Palliative Care’ and ‘Delirium’. A validated search filter for palliative care was used with minor adaptations.18 Delirium search terms were derived from recent relevant reviews.12,19 The search was conducted in June 2019 and updated in April 2020 using the full search and screening strategy (Supplemental File 1). A final rapid update (March 2021) was conducted using an accepted method20 (single reviewer, MEDLINE only, as it was the source of 83% of included studies in previous searches). Reference lists of included studies, relevant reviews identified through the search and delirium guidelines were examined for additional eligible studies.

Search results were screened in two stages: title and abstract and full text screening, using Covidence software.21 Two reviewers independently screened each result (IF, RW, JB, AH, PL) using Google Translate for non-English papers. At full text stage, reviewers selected a reason for exclusion from a hierarchical list. Where needed, translators, contacted through the Centre for Reviews and Dissemination (University of York), assisted in clarifying eligibility and enabling data extraction and risk of bias assessment. Disagreements were resolved through discussion to reach consensus or consultation with a third reviewer. When no full-text paper could be found, study authors were contacted.

**Data extraction**

Relevant data were extracted by one reviewer (IF) using a pre-piloted data extraction table in Excel22 and checked by a second reviewer (RW) (See Supplemental File 2 for data extraction items). Delirium occurrence was recorded as: point prevalence (delirium at a time point, such as admission); period prevalence (delirium on admission and during study period); or incidence (new cases during study period).

**Risk of bias assessment**

Validity and risk of bias were assessed independently by two reviewers (IF, GR, RW) using a modified version of the Quality in Prognosis Studies (QUIPS) tool.23 The following domains were assessed: study participation; attrition; risk factor measurement; confounding measurement and account; outcome measurement; analysis and reporting. Consensus on ratings was reached through discussion. QUIPS assessments were conducted only in relation to study data relevant to this review, therefore they should not be interpreted as assessments of the studies’ overall risk of bias per se. This informed decisions about whether study results should be included in meta-analysis; the narrative synthesis of results; and the GRADE (Grading of Recommendations Assessment, Development and Evaluation)24 ratings of the evidence for each risk factor.

**Data synthesis**

Clinical and methodological heterogeneity were assessed to decide whether to conduct meta-analyses. Studies evaluating the same risk factor were assessed to determine the extent of variability in relation to participants and settings; measurement of the risk factor and delirium outcome, including type of delirium occurrence; study design; risk of bias; and whether only univariate or multivariate analysis was conducted.25 Statistical heterogeneity was assessed using the I² statistic.26

The principal summary measures used in the review were odds ratios (95% confidence interval (CI)) for dichotomous risk factors and mean differences (95% CI) for continuous risk factors.27 Data were transformed to present a common statistic across studies where possible. Revman software28 was used to conduct meta-analyses using a random effects model (DerSimonian and Laird inverse variance) due to heterogeneity between studies.25 Where studies provided only the odds ratio and 95% confidence interval, the log odds ratio and standard error was calculated for all studies in the comparison and generic inverse variance was used for meta-analysis.25 Forest plots were used to present the results. Subgroup analyses were conducted to explore heterogeneity in relation to the type of delirium occurrence measured (point prevalence, period prevalence, incidence).

Narrative synthesis was used when meta-analysis could not be conducted. Studies examining each possible risk factor were grouped, their characteristics tabulated, and a common statistic presented across studies where possible. Potential moderator variables, including measurement of the risk factor and delirium outcome, were examined and a narrative interpretive summary was produced.29

**GRADE assessment**

The GRADE approach,24 with guidance on its adaptation for reviews of prognostic factor research,30,31 was used to assess the certainty of the body of evidence for the association of each risk factor with delirium. Downgrading of
the level of certainty was based on assessment of five domains (risk of bias, inconsistency, indirectness, imprecision and publication bias) and upgrading was based on large effects or exposure-response gradient.24

Results

Study selection

Twenty eight studies reported in 30 articles were included (Figure 1). Three studies were each reported in two articles32–38, two studies were reported in one article.39

Study characteristics

Supplemental File 3 shows detailed study characteristics. Included studies were from the USA (n = 7),37,40–45 Japan (n = 4),46–49 Italy32,33,50 and Spain (each n = 3),51–53 Canada,54,55 South Korea56,57 and the UK39 (each n = 2) and Taiwan,58 Germany,59 Mexico,60 Turkey61 and Switzerland (each n = 1).62 Twenty five studies were reported in English; two in Spanish52,53, one in Japanese.47

Most studies included inpatient specialist palliative care units in hospitals (n = 21)32,37,39,41,42,44,46–48,51,52 or hospice (n = 5).33,39,47,51,54 Three studies each included palliative care consultation teams40,45,49 and palliative care community services33,41,43

In 23 studies, all participants had a primary cancer diagnosis,32,33,37,40–42,46–62 three studies included cancer and non-cancer diagnoses39,43,44, two studies did not report diagnoses.39,45 Participants in 24 studies were in the late stages of illness (e.g. advanced or terminal cancer),32,33,37,39,42,46–62 while in the remaining four studies participants’ stage of illness was unclear.39,43–45

In 14 studies, only cross-sectional data was eligible for the review.32,33,37,39,41,42,44,47,48,50,51,56,57,60 There were two

Figure 1. PRISMA diagram.
prospective\textsuperscript{43,49}, one retrospective\textsuperscript{45} cohort studies (measuring delirium incidence); eight other prospective studies\textsuperscript{52–55,58,59,61,62}, three retrospective chart reviews\textsuperscript{36,37,40} (measuring delirium period prevalence). Sixteen studies conducted only univariate analysis (for the data eligible for the review)\textsuperscript{37,39–42,44,48,51–55,57,58,60,61} and 12 also conducted multivariate analysis.\textsuperscript{32,33,39,43,45–47,49,50,56,59,62}

**Risk of bias within individual studies**

Table 1 presents the ratings for the QUIPS risk of bias domains for individual studies.

| Study                          | 1. Study participation | 2. Study attrition | 3. Risk factor measurement | 4. Outcome measurement | 5. Study confounding | 6. Statistical analysis and reporting |
|-------------------------------|------------------------|-------------------|---------------------------|------------------------|---------------------|-----------------------------------|
| Barahona et al.\textsuperscript{51} | High                   | N/A               | High                      | Moderate               | High                | High                              |
| Braiteh et al.\textsuperscript{40} | Moderate              | Low               | High                      | Moderate               | High                | High                              |
| Caraceni et al.\textsuperscript{50} | Moderate              | N/A               | Moderate                  | Low                    | Moderate            | Moderate                          |
| De la Cruz et al.\textsuperscript{37,38} | Low                   | Low               | Low                       | Moderate               | High                | High                              |
| Diaz Garcia et al.\textsuperscript{52} | High                  | Moderate          | Moderate                  | Moderate               | Moderate            | High                              |
| Fadul et al.\textsuperscript{41} | Moderate              | N/A               | Low                       | Moderate               | High                | High                              |
| Fang et al.\textsuperscript{58}   | High                   | Low               | Low                       | Moderate               | High                | High                              |
| Farriols Danés et al.\textsuperscript{53} | Low                   | Low               | High                      | Moderate               | High                | High                              |
| Gagnon et al.\textsuperscript{54}  | Low                    | Moderate          | Moderate                  | Moderate               | Moderate            | High                              |
| Kang et al.\textsuperscript{56}   | Moderate              | N/A               | Moderate                  | Low                    | Moderate            | Moderate                          |
| Kim et al.\textsuperscript{37}    | Moderate              | N/A               | High                      | Moderate               | High                | High                              |
| Lawlor et al.\textsuperscript{55}  | Low                   | Low               | Moderate                  | Moderate               | High                | High                              |
| Matsuo et al.\textsuperscript{49}  | Low                   | Low               | Moderate                  | Moderate               | Moderate            | Moderate                          |
| Matsuoka et al.\textsuperscript{46} | High                  | Low               | Moderate                  | Moderate               | Moderate            | Moderate                          |
| Mercadante et al.\textsuperscript{32,34} | Moderate            | N/A               | Moderate                  | Low                    | Low                 | Moderate                          |
| Mercadante et al.\textsuperscript{33,35} | High                  | Moderate          | Moderate                  | Moderate               | Moderate            | Moderate                          |
| Minagawa et al.\textsuperscript{48} | Moderate              | N/A               | Moderate                  | Moderate               | High                | High                              |
| Morita et al.\textsuperscript{47}  | High                   | N/A               | Moderate                  | High                   | High                | High                              |
| Plaschke et al.\textsuperscript{59} | Moderate              | High               | Moderate                  | Moderate               | Moderate            | Moderate                          |
| Rodriguez-Mayoral et al.\textsuperscript{40} | Moderate            | N/A               | Moderate                  | Low                    | High                | High                              |
| Sarhill et al.\textsuperscript{42}  | Moderate              | N/A               | Moderate                  | High                   | High                | High                              |
| Seiler et al.\textsuperscript{62}  | High                   | High               | Moderate                  | High                   | High                | Moderate                          |
| Senel et al.\textsuperscript{61}   | Moderate              | Low               | High                      | Moderate               | High                | High                              |
| Slatore et al.\textsuperscript{43}  | High                   | High               | Moderate                  | Moderate               | High                | Moderate                          |
| Spiller and Keen\textsuperscript{39} | Moderate              | N/A               | High                      | Moderate               | Moderate            | Moderate                          |
| Spiller and Keen\textsuperscript{39} | Moderate              | N/A               | High                      | Moderate               | High                | High                              |
| Stillman and Rybicki\textsuperscript{44} | High                  | N/A               | Moderate                  | Moderate               | High                | High                              |
| Zimmerman et al.\textsuperscript{45} | Moderate              | Low               | Moderate                  | High                   | Moderate            | Low                               |

Level of assessed risk of bias = low (green)/moderate (amber)/ high (red); N/A = Not applicable (white). Several studies excluded patients at high risk of delirium such as those with dementia/cognitive impairment (five studies\textsuperscript{46,52,56,59,61}) and severely ill/dying patients (seven studies\textsuperscript{32,33,42,46,48,52,56}). Routine data on risk factors were often used and their measurement not clearly defined. The timing of exposure in relation to outcome measurement was unclear in many studies (cross-sectional or measuring delirium period prevalence)\textsuperscript{39,47,57,59,61,62} All included studies used validated delirium assessment tools or criteria but the methods and frequency of assessment were variable.
Sixteen studies included only univariate data on the association between risk factors and delirium, so made no adjustment for confounding. Many of the studies which conducted multivariate analysis had adjusted for some, but not all, important potential confounding factors. Several included studies selectively reported results, including six studies which only reported multivariate analysis results that were statistically significant.

Potentially modifiable risk factors. Additional forest plots for study results included in meta-analyses are presented in Supplemental File 4. Due to heterogeneity between studies, most results could not be combined and are tabulated in Supplemental File 5.

Medications and treatment risk factors. Opioids \((n=12)\): Three studies reported statistically significant positive associations between opioid use and delirium in univariate analysis, which persisted in multivariate analysis in Matsuo et al.'s study (OR 3.7, 95% CI 1.0, 13.0) but not in Matsuoka et al.'s study (OR 2.85, 95% CI 0.82, 9.90). Plaschke et al. reported no statistically significant association with morphine use.

Regarding opioid dose \((n=5)\), two studies reported higher mean opioid dose in the delirium group and one reported a higher median dose, although these results were not statistically significant. Morita et al. reported that higher opioid use (cut off unclear) was significantly associated with delirium and Mercadante et al. reported a statistically significant correlation between opioid dose and delirium on admission.

All three studies examining opioid toxicity reported a statistically significant positive association with delirium. Steroids \((n=6)\): Four out of five studies examining steroid use \((yes/no)\) in univariate analysis reported a positive association with delirium which reached significance in three of the studies. Two studies used multivariate analysis and found no statistically significant association. In Matsuo et al.'s study, no statistically significant association was found between higher dose of corticosteroid treatment \((>=3\ mg\ initial\ daily\ dose\ as\ betamethasone\ equivalent)\) and delirium incidence (unadjusted OR 0.90, 95% CI 0.43, 1.88).

Anticholinergics \((n=6)\): Five studies reported mixed results from univariate analysis of association between anticholinergic medications/load and delirium. Zimmerman et al. reported that delirium incidence following hospital admission was significantly higher in participants whose Anticholinergic Risk Scale score increased from baseline in multivariate analysis (OR 1.43, 95% CI 1.04, 1.94).

Anxiolytics/hypnotics \((n=4)\): Results of four studies examining anxiolytics/hypnotics were mixed, but overall suggested a small positive association with delirium. These results could not be pooled due to differing definitions of medication types.

Other medications: Two studies reported statistically significant associations of antiepileptic/anticonvulsant drugs with delirium in univariate analysis but significance was not retained in multivariate analysis in Matsuo et al.'s study (OR 3.42 95% CI 0.58, 20.01). Antipsychotics and beta blockers were each examined in one study with statistically significant associations with delirium reported in univariate analysis. Significance was retained in multivariate analysis for beta blockers (OR 3.95 95% CI 1.642, 9.479) but not for antihistamine drugs (OR 1.28 95% CI 0.14, 11.37). Plaschke et al. found no association between antibiotic use and delirium.

In univariate analysis, Şenel et al. reported a statistically significant positive association between polypharmacy (more than three drugs) and delirium period prevalence (unadjusted OR 26.39, 95% CI 12.70, 54.82).

Cancer treatments \((n=4)\): In univariate analysis, two studies found non-significant positive associations between radiotherapy and delirium point prevalence. Mixed results were reported for hormonal therapy (two studies) and chemotherapy (three studies). One study found no significant association of delirium with blood transfusion.

Physiological risk factors. Nutrition-related risk factors \((n=11)\): The pooled mean difference in the Edmonton Symptom Assessment System (ESAS) lack of appetite score between those with and without delirium on admission from three studies was statistically but not clinically significant (less than 1 point difference in ESAS score). Results from two further studies of ESAS lack of appetite score, not included in meta-analysis, were mixed, as were the results of two studies examining the association of malnutrition and of low Body Mass Index with delirium. Two studies examining anorexia in univariate analysis, and cachexia in multivariate analysis (OR 3.44, 95% CI 1.55, 7.63 and OR 3.24, 95% CI 0.747, 14.096) suggested an association with delirium.

Infection-related risk factors \((n=7)\): Three studies examining association between infection and delirium reported statistically significant positive associations in univariate analysis, although this was not retained in Matsuo et al.'s multivariate analysis (OR 2.83, 95% CI 0.79, 10.12). Two studies reported statistically significant positive associations between fever and delirium. One study found a statistically significant positive association between sepsis and delirium period prevalence; but no association with pneumonia.

Dehydration \((n=5)\): Five studies examining the association between dehydration and delirium in univariate
analysis,33,39,46,61 two using multivariate analysis, (OR 5.16, 95% CI 1.83, 14.59 and OR 2.50, 95% CI 1.17, 5.34) reported positive associations.

**Hypoxaemia (n = 5):** Of the five studies which examined association between hypoxaemia and delirium in univariate analysis,39,46,49,57,61 four reported positive associations, of which three reached significance. However, in the one multivariate analysis46 this was no longer associated (OR 0.93, 95% CI 0.28, 3.13).

**Liver and renal dysfunction (n = 4):** Four studies reported on risk factors related to liver and renal dysfunction.47,49,61,62 In univariate analysis, delirium was positively associated with several markers of liver dysfunction including raised bilirubin47,49,61 and low serum albumin levels.47,49 One study reported a non-significant positive association with liver failure62 and one reported a statistically significant association with renal and/or liver failure.61 In multivariate analysis, one study62 reported no association between delirium period prevalence and chronic renal disease (OR 0.81, 95% CI 0.26, 2.53), but a statistically significant positive association with acute renal failure (OR 6.79, 95% CI 1.06, 43.41).

**Leucopoenia (n = 4):** In univariate analysis, three out of four studies reported positive associations that did not reach significance between delirium and high leucocyte count47,49,50,59, two studies49,50 found no association with low lymphocytes.

**Calcium/sodium abnormalities (n = 2):** Two studies reported no significant associations of calcium and sodium abnormalities with delirium in univariate analysis.47,49

**Oedema (n = 3):** In univariate analysis, no significant association was found between lung oedema and delirium in one study.62 In one study, no association was found with peripheral oedema,49 but another found very increased odds of delirium for those with oedema in the lower leg or upper arm (OR 10.92, 95% CI 5.21, 22.89).47

**Pleural effusion (n = 2):** No significant associations were found between delirium and pleural effusion in two studies.49,62

**Anaemia (n = 2):** Two studies reported non-significant positive associations of anaemia with delirium period prevalence.46,61

**Sensory impairment (n = 1):** One study reported statistically significant associations of hearing impairment62 (OR 3.52, 95% CI 1.721, 7.210) and vision impairment62 (OR 3.15, 95% CI 1.765, 5.607) with delirium period prevalence in multivariate analysis.

One study each reported statistically significant associations of numbness47 and pressure sores62 with delirium.

**Symptom risk factors. (Reported in order of ESAS, except loss of appetite reported in nutrition-related risk factors above)**

**Symptom burden (total ESAS score):** Two studies examined the association of symptom burden (total ESAS score) and delirium with mixed results.32,33

**Pain (n = 8):** Pooling three studies32,33,56 comparing the ESAS pain scores of patients with and without delirium on admission found no difference (Figure 3). Two studies37,59 reported a higher mean pain score in participants without delirium during the study whereas two studies53,62 reported a positive association of pain with delirium period prevalence in univariate analysis, which was close to significance in Seiler et al.’s62 multivariate analysis (OR 2.42, 95% CI 0.95, 6.23, p = 0.07). Overall, the evidence on the association of pain with delirium was mixed.

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Figure 2. Forest plot: ESAS lack of appetite and delirium point prevalence (mean difference).

Figure 3. Forest plot: ESAS pain score and delirium point prevalence on admission (mean difference).
Fatigue/weakness \((n = 5)\): Overall, the evidence from five studies did not find a significant association of fatigue/weakness with delirium \((n = 5)\) (Appendices 4 and 5).

Drowsiness \((n = 5)\): In univariate analysis in four studies, the evidence of an association between drowsiness and delirium was mixed but multivariate analysis in three studies found statistically significant positive associations (Appendices 4 and 5).

Nausea \((n = 6)\): Six studies that examined the association of nausea and delirium in univariate analysis reported mixed results.

Breathlessness \((n = 7)\): Meta-analysis of mean difference in dyspnoea ESAS score in three studies found no association with delirium \((0.05, 95\% \text{ CI } -0.56, 0.65)\) (Supplemental File 4). Three of the four studies reporting unadjusted odds ratios reported positive associations of breathlessness with delirium of variable size.

Depression, anxiety and decreased wellbeing: Overall, the evidence from five studies examining depression and anxiety did not support a clinically significant association with delirium. Four studies examining the association of decreased wellbeing with delirium had mixed results.

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Sleep disturbance \((n = 5)\): Combined mean difference in ESAS sleep disturbance score between those with and without delirium on admission from two studies was statistically, but not clinically, significant (Figure 4). One study reported a non-significant negative association between ESAS sleep disturbance and delirium period prevalence. One study reported a non-significant positive association of insomnia with delirium incidence. Slatore et al. reported a hazard ratio for developing delirium for each 1 point worse sleep quality in the last month as 2.37 \((95\% \text{ CI } 1.50, 3.74)\).

Constipation \((n = 4)\): Two studies reported statistically significant positive associations between constipation and delirium in univariate analysis and two studies found no association.

Behavioural disorders: Association of smoking, alcohol misuse and substance use disorder with delirium were examined in one study each and no statistically significant associations were found.

Performance status, illness severity and prognostic assessments. Eighteen studies reported that lower performance status was strongly associated with delirium, using either Karnofsky Performance Status (eight studies) \(32,33,44,48,50,53,59,60\); Eastern Cooperative Oncology Group (ECOG) Performance Status (seven studies) \(37,39,46,49,56,57,60\) or the Palliative Performance Scale (five studies) \(37,49,51,52,61\). One study reported a statistically significant positive association between immobilisation and delirium period prevalence in univariate analysis.

Two studies found no significant difference in Charlson Comorbidity Index scores. One study found no statistically significant association between illness severity (APACHE III) and delirium incidence; while one study each found that admission for end of life care and higher palliative prognostic index scores were associated with delirium.

Non-modifiable risk factors. Additional forest plots for study results included in meta-analyses are presented in Supplemental File 6. Results are tabulated in Supplemental File 7.

Age. \((n = 18)\). Meta-analysis of mean difference in age reported by nine studies suggested that participants with delirium were on average 3.08 \((95\% \text{ CI } 1.01, 5.16)\) years older than those without delirium (Figure 5). This was higher in studies measuring delirium point prevalence \((5.62 \text{ years}, 95\% \text{ CI } 2.97, 8.27 \text{ years})\). Unadjusted odds ratios from six studies and adjusted odds ratios from four studies reported either a small association of older age with delirium or no significant association.

Sex. \((n = 18)\). The summary unadjusted odds ratio from 15 studies suggests that male palliative care patients were slightly more likely to have delirium than female patients \((OR 1.39, 95\% \text{ CI } 1.23, 1.57)\) (Figure 6). Results of three further studies not included in meta-analysis were consistent with this.

Cancer-related risk factors. Three cancer-related risk factors were examined in this review: lung cancer \((n = 12)\); brain cancer/brain metastases \((n = 12)\) and metastases (overall) \((n = 4)\). Patients with lung cancer may be slightly more likely to have delirium than those without.
Twelve studies examined the association between primary brain cancer and/or brain metastases and delirium. Positive associations were found in meta-analyses of univariate analyses between delirium and primary brain cancer (OR 2.01, 95% CI 0.98, 4.14) and brain metastases (OR 3.16, 95% CI 1.85, 5.40) (Supplemental File 6). Seiler et al. found a positive association with primary brain cancer in multivariate analysis (OR 3.63, 95% CI 1.03, 12.77). Three further univariate analyses of brain metastases, from
studies not included in meta-analysis,\textsuperscript{55,49,58} two studies that combined primary brain cancer and brain metasta-
ses as a single risk factor,\textsuperscript{55,61} reported mixed results.
Seven studies reported positive associations bet-
 tween other neurological/ cerebral risk factors and
delirium.\textsuperscript{39,40,44,46,51,61,62} As these were defined in dif-
ferent ways they could not be combined for meta-analysis. One
study each reported a statistically significant association of
‘neurological diseases’\textsuperscript{61}; ‘cerebral disease’\textsuperscript{39}; ‘focal neuro-
logical deficit’\textsuperscript{44} and ‘myoclonus’\textsuperscript{40} with delirium.

In meta-analysis of univariate data from four studies,
presence of metastases (overall) was not associated with
delirium period prevalence (OR 0.83, 95% CI 0.66, 1.05)
(Supplemental File 6).\textsuperscript{52,53,55,61}

\textbf{GRADE assessment of the certainty of the}
evidence for risk factors’ association with
delirium

The certainty of the evidence for the following risk factors
was graded as low: gender, lung cancer, metastases (over-
all), primary brain cancer, performance status, opioid use,
dehydration, infection and drowsiness. For all other risk
factors, certainty was rated as very low (Supplemental File
8). The evidence for most risk factors was downgraded for
risk of bias, based upon the QUIPs assessments and lack
of adequate adjustment for confounding factors in analy-
sis. The evidence for many risk factors was also down-
graded for inconsistency, due to unexplained heterogeneity
between study results, and for imprecision of the results.\textsuperscript{24}

\section*{Discussion}

\textbf{Main findings}

We found that the evidence from 28 included studies
regarding the association of possible risk factors with
delirium in adults in palliative care settings was limited,
particularly for many potentially modifiable risk factors,
and was of low or very low certainty.

In relation to potentially modifiable risk factors, there is
evidence of positive associations between delirium and
both opioids and lower performance status and suggestive
evidence for dehydration, hypoxaemia, sleep disturbance,
liver dysfunction and infection. Positive associations with
delirium were reported in only one study for each of the
following: polypharmacy, sensory impairment, immobility,
pressure sores and indwelling catheter use.

There was more mixed evidence about the association
delirium with pain, dyspnoea, anticholinergics, drowsi-
ness, anxiolytics/ hypnotics, steroid use, constipation and
nutrition-related risk factors.

In relation to non-modifiable risk factors, the evidence
suggests positive associations of delirium with older age;
male sex; primary brain cancer or brain metastases and
lung cancer.

\textbf{Strengths and limitations of the review}

To our knowledge, this is the first systematic review con-
ducted of risk factors for delirium in palliative care settings.
Rigorous review methods were used. Particular strengths
were the inclusion of studies that only used validated delir-
ium assessment tools or criteria; inclusion of non-English
language papers; screening and risk of bias assessment con-
ducted by two independent reviewers and GRADE assess-
ment of the certainty of evidence for each risk factor.\textsuperscript{24}

Most included studies were not high quality cohort
studies comparing delirium incidence between those
exposed/ not exposed to the risk factor. Identifying delir-
ium risk factors was not the primary aim of most included
studies. Many provided only cross-sectional data, or
measured delirium period prevalence, so timing of risk
factor exposure in relation to delirium development was
unclear. Little evidence was reported on several poten-
tially modifiable risk factors recommended in delirium risk
reduction guidelines.\textsuperscript{64,65}

Delirium can result from a complex interplay between
multiple risk factors\textsuperscript{8} and this was not adequately accounted
for in the included studies which mostly used only unvari-
ate analyses. Due to the multiple risk factors for delirium, it
is difficult to account for all potential confounding and, as
Zaal et al.\textsuperscript{9} (p. 69) noted, ‘it is poorly established which con-
founders should be incorporated in multivariable risk fac-
tors models’ for delirium. Multivariate analysis adjusted for
some, but not all, potentially important confounding fac-
tors. For example, those examining associations between
pain and delirium did not adjust for opioid use.

We separately reported the results for those risk fac-
tors that are clearly non-modifiable (e.g. age, sex) and
those which may potentially be modifiable. However,
what is modifiable is uncertain, for example, it might not
be possible to modify risk factors such as liver and renal
dysfunction and performance status. In palliative care
contexts, the modification of many risk factors may not be
possible due to factors such as the patient’s stage of ill-
ness and their goals of care.\textsuperscript{11}

Most studies in this review were conducted in in-
patient palliative care settings with participants with late-
stage cancer, so results may be less generalisable to other
patients receiving palliative care services. The definition
of the eligible population as patients in receipt of special-
ist palliative care services could be clearly operationalised
to conduct this review. However, it led to the exclusion of
some possibly relevant studies, such as those of delirium
risk factors for terminally ill patients in the general hospi-
tal setting.\textsuperscript{66,67}

\textbf{What this study adds}

Delirium guidelines, not specific to palliative care con-
texts, such as NICE\textsuperscript{64} and SIGN,\textsuperscript{65}and systematic reviews of
multicomponent interventions,\textsuperscript{6,7} recommend delirium
risk reduction through targeting modifiable risk factors. The evidence from this review suggests positive associations between delirium and opioid use, higher opioid dose and toxicity in palliative care settings. This supports the importance of medication review and use of the minimum effective dose, in line with delirium guidelines. The limited evidence of associations of other modifiable risk factors with delirium, provides some support for targeting risk factors included in guidelines and interventions from other settings including dehydration, hypoxaemia, sleep disturbance and infection, to reduce delirium in palliative care.

The low or very low certainty of the evidence must be taken into account in drawing clinical implications from our findings. Several potentially modifiable risk factors targeted in guidelines and interventions from other settings including sensory impairments, mobility, catheter use and polypharmacy, were each examined in only one study, which reported positive associations with delirium. A systematic review found these to be statistically significant risk factors for delirium incidence for older hospitalised patients. We found mixed evidence regarding several other risk factors—pain, constipation and nutrition—which are commonly targeted in delirium prevention strategies. This highlights the need for further, high-quality research focussed on the association of potentially modifiable risk factors with delirium in palliative care settings.

Although performance status was strongly associated with delirium in this review, it is not a single modifiable risk factor. It could be useful, in conjunction with evidence on other modifiable/non-modifiable risk factors, in developing predictive models of patient subgroups most likely to develop delirium. In relation to non-modifiable risk factors, this review’s results support the association between older age and delirium found in other settings. Associations between delirium and male sex, brain cancer/metastases and lung cancer were also identified in palliative care contexts. Notably, dementia, which is strongly associated with delirium in other settings, was only examined by one study in this review. However, as delirium prevalence in palliative care patients is very high (58%–88% in the last weeks of life), it is arguably more of a priority to develop population-level preventative interventions targeting modifiable risk factors, than to predict subgroups of patients at elevated risk in order to target interventions for them.

In treating an established episode of delirium, modifiable causes are also targeted (in accordance with the patient’s goals of care), to attempt to reduce the length and severity of the episode. A study in an acute palliative care unit found 49% of delirium episodes could be reversed. Although the primary focus of our review was on factors affecting the risk of developing delirium, its findings could also be used to inform further research to identify modifiable factors to target in delirium treatment. Several additional studies have investigated delirium reversibility through systematic investigation of multiple precipitating risk factors in palliative care patients who have developed delirium. Their data were excluded from this review because they did not include a comparator group without delirium, but may be informative in research to identify factors associated with delirium reversibility.

Conclusion

The limited evidence from this systematic review offers support for the use of interventions that target modifiable risk factors to reduce the risk of delirium for palliative care patients. However, there is a need for high-quality prospective cohort studies with more comprehensive and robust delirium risk factor measurement along with adequate adjustment for important confounding factors through multivariate analysis. This will enable much greater certainty in the evidence regarding the strength of the association of different risk factors with delirium, to inform the design of multicomponent interventions to reduce risk of delirium, and clinical decision-making regarding competing risks, in the palliative care context.

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Authorship

IF, TS, MJ, RW, JB, AH, PL, GR, SB and NS made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data. IF, RW, JB, AH and PL screened papers for inclusion in the review. IF, GR and RW conducted risk of bias assessment. IF drafted the article and all other authors revised it critically. All authors approved the version to be published.

Declaration of conflicting interests

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No ethical approval was required for this research, as it was a review of existing published articles with no new primary data collected.

ORCID iDs

Imogen Featherstone https://orcid.org/0000-0002-9042-7600
Miriam Johnson https://orcid.org/0000-0001-6204-9158
Rebecca Woodhouse https://orcid.org/0000-0001-8374-8994
Jason W Boland https://orcid.org/0000-0001-5272-3057
Annmarie Hosie https://orcid.org/0000-0003-1674-2124
Peter Lawlor https://orcid.org/0000-0001-7319-1395

Data management and sharing

All of the papers included in this review are available through their respective journals.

Supplemental material

Supplemental material for this article is available online.

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