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REVIEW

Factors associated with prolonged delirium: a systematic review

Monidipa Dasgupta[1,2] and Loretta M. Hillier[2]

[1] *Division of Geriatric Medicine, Department of Medicine, The Schulich School of Medicine and Dentistry, The University of Western Ontario, London, Ontario, Canada*
[2] *Specialized Geriatric Services and Aging, Rehabilitation and Geriatric Care Research Centre of the Lawson Health Research Institute, St. Joseph's Health Care, Parkwood Hospital, London, Ontario, Canada*

ABSTRACT

Background: Delirium frequently accompanies acute illness. With treatment of the illness, some individuals recover from delirium while for others the symptoms persist. It is not understood why some individuals improve but others do not. The purpose of this paper is to review systematically what is known about the factors associated with the persistence of delirium.

Methods: A medical literature search was conducted using several bibliographic databases, supplemented by manual searches of the references. English or French studies were included if they compared two groups of delirious individuals in delirium duration or persistence up to six months after the onset of delirium, diagnosed prospectively with the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria (or a scale derived and validated against the DSM). Information was collected on the association between possible non-therapeutic prognostic variables and delirium persistence.

Results: Twenty-one observational studies were included, in various settings (e.g. mixed medical-surgical, medical or geriatric, surgical, psychiatric, cancer or palliative care units). Variables assessed included patient characteristics (e.g. age, dementia, medical comorbidity, functional status), delirium characteristics (e.g. presence of hypoactive symptoms, delirium severity) and illness characteristics (e.g. severity of illness, and underlying acute illness). Overall, studies suggested that delirium is often persistent at discharge or beyond. Persistence was associated with dementia, increasing numbers of medical conditions, increasing severity of delirium, hypoactive symptoms and hypoxic illnesses.

Conclusions: Preliminary findings suggest that some factors may identify those at risk for persistent delirium; however, more research is needed.

Key words: prognosis, confusion, complications, systematic review

Introduction

Delirium is a frequent accompaniment of acute illness, occurring in 11–50% of hospitalized older adults (Lipowski, 1987; Siddiqi *et al.*, 2006). Delirious individuals undergo acute changes in cognitive functioning characterized by reduced ability to sustain attention, disorganized thinking, disorientation, delusions, perceptual disturbances, impaired memory, speech, psychomotor activity, and sleep (Lipowski, 1987; American Psychiatric Association, 1994). Delirium is also associated with multiple adverse outcomes including increased length and cost of hospitalization, functional and cognitive decline, institutionalization, and mortality (Francis and Kapoor, 1992; Rockwood *et al.*, 1999; Marcantonio *et al.*, 2000; McCusker *et al.*, 2002; Pitkälä *et al.*, 2005; Adamis *et al.*, 2006; Inouye, 2006).

Although it is well accepted that delirious individuals as a whole do worse than non-delirious hospitalized individuals, it is not well understood why some individuals recover from their delirium while others do not (Andrew *et al.*, 2005). Delirium has been described as a potentially reversible condition with treatment of the underlying condition (Lipowski, 1987; Rockwood, 1989). However, as demonstrated in

Correspondence should be addressed to: Dr. Monidipa Dasgupta, Division of Geriatric Medicine, Rm. A3–125, St. Joseph's Health Care, 268 Grosvenor St., London, ON N6A 4V2, Canada. Phone: +1 (519) 646–6188. Email: monidipa.dasgupta@sjhc.london.on.ca. Received 25 Jun 2009; revision requested 5 Aug 2009; revised version received 4 Nov 2009; accepted 6 Nov 2009. First published online 21 January 2010.

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a recent systematic review (Cole *et al.*, 2009), delirium symptoms often persist at discharge or beyond (Marcantonio *et al.*, 2000; Kelly *et al.*, 2001; Kiely *et al.*, 2004; Adamis *et al.*, 2006). The duration of a delirium episode is variable, with studies reporting delirium lasting 60 days or more (Koponen *et al.*, 1989; Manos and Wu, 1997). Persistent delirium symptoms are also associated with a diminished ability to perform basic and instrumental activities of daily living compared to an individual's baseline (pre-delirious) abilities and increased mortality (Marcantonio *et al.*, 2000; McCusker *et al.*, 2003, Kiely *et al.*, 2006; 2009; Cole *et al.*, 2009).

In today's medical environment, in which there is constant pressure to discharge individuals quickly from acute care, there is often not enough time to observe delirious individuals to determine whether their delirium will resolve. Clinicians often have to inform family members of the potential for recovery and make decisions about potential rehabilitation and/or other discharge destinations. Unfortunately, little is known about how to predict whether a delirious individual will recover from their delirium. The purpose of this paper is to review systematically what is known about the factors associated with the persistence of delirium.

Methods

PubMed was searched for English or French studies (1960 to February 2009) using the Medical Subject Heading (MeSH) "delirium" or "confusion" and "prognosis" or "risk factors". Using this same search strategy, Medline, CINAHL, Embase, PsychoInfo and the Cochrane databases were also searched. Manual searches of the references of retrieved articles were also conducted. Both authors independently performed these searches.

Inclusion/exclusion criteria

Citations (titles and abstracts) were reviewed independently by both authors and selected for review of the full-text article based on their potential to meet the inclusion criteria as described below. Each author independently reviewed the full-text articles for inclusion. All disagreements were resolved by consensus. When required the authors also attempted to contact original authors of included articles for additional information.

Studies were included in the review if they: (i) included original data on adult patients (19 years or older); (ii) compared at least two groups of delirious patients in delirium duration or persistence with observation periods extending up to six months after the onset of delirium; (iii) prospectively diagnosed delirium with the Diagnostic and Statistical Manual of Mental Disorders (DSM) III or IV criteria (American Psychiatric Association, 1987; 1994) or a scale derived from and validated against the DSM criteria; (iv) defined delirium duration as the time at which delirium was no longer present according to DSM or a DSM-derived and validated scale; (v) enrolled patients consecutively; and (vi) provided results on statistical significance between the measure of delirium duration and the independent variable (any non-therapeutic prognostic variable). Intervention studies could be included if the intervention had no effect on delirium duration or if results were adjusted for intervention status.

Studies were excluded from the review when they: (i) only provided data on comparisons between delirious patients and another patient group, which included non-delirious patients; (ii) did not use DSM or DSM-derived and validated criteria to diagnose delirium and how long it lasted; or (iii) used retrospective methods to diagnose delirium.

Data extraction

Information was collected on: (i) type of patient population; (ii) the effective sample size (i.e. the number of delirious individuals being compared, which may not be the same as the entire study sample if the study also included non-delirious controls); (iii) which comparator variables were assessed and how these were measured; (iv) study findings (bivariate or multivariate analyses); and (v) how and when delirium duration was defined. Studies were further divided according to whether they assessed delirium duration in the short-term (within three months of delirium diagnosis) or in the longer-term (at three to six months after delirium diagnosis). For the purposes of this review, data from studies on the effect of a specific comparator variable on delirium duration were included in the results tables when the effect of the comparator variable was assessed in at least two studies (comparator variables that were assessed in only one study were not included). Data were extracted by one author (MD) and reviewed by the second author.

Statistics

Although no pooling of data was conducted, simple statistics were abstracted from the individual studies where available. Odds ratios (ORs), HRs (hazard ratios), relative risks (RRs), and confidence intervals (or if unavailable, p-values) were abstracted when provided by the original studies. Generally (see Tables 2 and 3), ORs (or other measures of strengths of association) for delirium persistence were listed. If ORs were not provided but adequate data were available, the ORs were calculated (i.e. odds of persistence given risk factor / odds of persistence

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without risk factor). As presented in Table 4, one of the studies provided HRs for delirium resolution and ORs for delirium resolution from other studies were listed. If studies included in this table provided ORs for delirium persistence (instead of resolution), ORs were calculated for resolution as 1/OR for persistence.

Study quality assessment

According to the evidence-based medicine (EBM) working group (Guyatt *et al.*, 2002), four criteria can be used to judge the validity of prognostic studies: (i) whether a representative patient population is enrolled; (ii) whether there was an objective and unbiased outcome assessment; (iii) whether there was adequate follow-up; and (iv) whether the two groups being compared are homogenous with respect to prognostic risk. The inclusion criteria for this review mandated consecutive enrollment (albeit in differing patient populations), and the use of a DSM (or Confusion Assessment Method) derived measure of delirium duration. In this manner, the first two criteria for validity were consistently met across included studies (although blinding was rarely commented upon in the studies). The last two criteria were not uniformly met by all studies. The extent of follow-up was not always commented upon in studies. Homogeneity of prognostic risk, which was judged by whether studies performed multivariable analyses incorporating other possible risk factors, was also not always addressed. These methodological features are therefore discussed when looking at the quality of individual studies. Both authors also independently judged studies using a rating scale similar to that used by Elie and colleagues (1998) in their systematic review of delirium risk factors. With this scale, studies are specifically assessed on whether they provide an adequate description of: (i) patient groups; (ii) selection process; (iii) methods to characterize both groups; (iv) methods to define risk factors; (v) presence of blinding; (vi) study power; (vii) confidence intervals and strength of association; and (viii) adjustment for confounders. This latter criterion was felt to be similar to one of the EBM-working group criteria (i.e. whether the groups are homogenous with respect to prognostic risk).

Results

A total of 2260 citations (titles and abstracts) were reviewed, from which 124 articles were retrieved for full-text review (see Figure 1). The level of initial agreement between authors in the studies to be retained for the review was 89% ($\kappa = 0.72$; Streiner, 1995). After consensus discussion, 103 articles were excluded, leaving 21 articles that met the inclusion criteria, of which 19 involved the enrollment of unique study populations. Two studies overlapped in some part of their patient populations (McCusker *et al.*, 2003; Cole *et al.*, 2007).

Methodological features

There was generally good agreement between both authors on study quality ($\kappa = 0.74$), and methodological features. All of the included

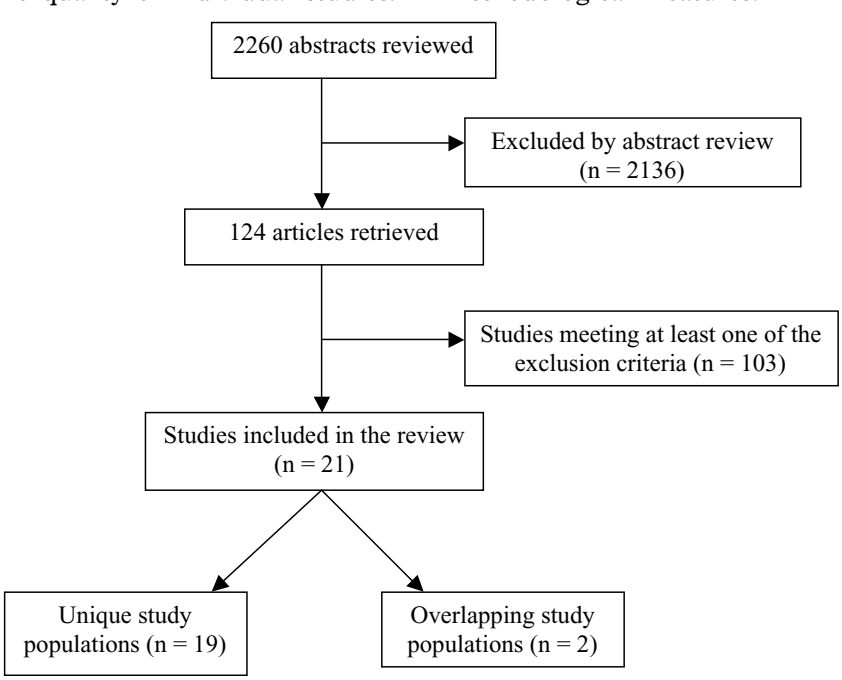


Figure 1. Selection of studies for review

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studies were observational. All provided adequate descriptions of the study population profiles and excluded individuals unable to communicate because of medical conditions such as aphasia or language limitations. All studies characterized the selection process (consecutive enrollment), and had structured definitions of the two groups (persistent or resolved delirium). Studies differed in how they measured risk (prognostic) factors, with some, but not all, studies using specific criteria to measure prognostic factors. Only three studies (16%) reported on blinding (McCusker *et al.*, 2003; Cole *et al.*, 2007; Inouye *et al.*, 2007). None of the studies provided information on the sample size needed to detect differences in delirium duration and many studies had primary objectives other then looking at determinants of delirium duration.

When looking specifically at the dependent variable – delirium duration – all of the studies provided information on clinically significant associations. Three studies (Koponen *et al.*, 1989; Adamis *et al.*, 2006; Leonard *et al.*, 2008) did not provide an estimate of (or enough data to calculate) the strength of association, such as an odds ratio, relative risk, hazard ratio, or difference of means. Six studies (29%) reported confidence intervals around some of the variables assessed and their associations with delirium duration (Levkoff *et al.*, 1994; Lawlor, 2000; Kiely *et al.*, 2004; Cole *et al.*, 2007; Inouye *et al.*, 2007; Sagawa *et al.*, 2009). Seven (33%) conducted multivariate or adjusted analyses when looking specifically at determinants of duration (Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Kiely *et al.*, 2004; Adamis *et al.*, 2007; Cole *et al.*, 2007; Leonard *et al.*, 2008; Sagawa *et al.*, 2009). Selection bias was minimized because consecutive enrollment was required for all of the studies reviewed.

Information on loss to follow-up of delirious individuals because of death, acute hospitalization or other causes was described in six (29%) studies (Oloffson *et al.*, 1996; Camus *et al.*, 2000; McCusker *et al.*, 2003; Kiely *et al.*, 2004; Speciale *et al.*, 2007; Sagawa *et al.*, 2009), and ranged from 4% to 50%. Loss to follow-up from death specifically ranged from 5% to 26%. Six (29%) studies included data on individuals who had died (Rudberg *et al.*, 1997; Lawlor *et al.*, 2000; Kelly *et al.*, 2001; Adamis *et al.*, 2006; 2007; Leonard *et al.*, 2008). Participation rates were provided in four studies (16%) (Levkoff *et al.*, 1994; Kiely *et al.*, 2004; McAvay *et al.*, 2006, Inouye *et al.*, 2007). In one of these studies, participation rates were provided in an earlier publication (Levkoff *et al.*, 1992). However, three of these studies (Levkoff *et al.*, 1994; McAvay *et al.*, 2006, Inouye *et al.*, 2007) included non-delirious individuals in the non-participation or refusal rate, thus making it difficult to know the participation rates of specifically delirious individuals.

All of the studies involved hospitalized inpatients, although they enrolled different populations including medical, geriatric or surgical patients, mixed surgical and medical, psychiatric (or referred to psychiatry services), hospitalized nursing home patients, individuals with cancer or in palliative care units, and patients from a post-acute care or rehabilitation setting (see Table 1). Only one study included patients from an intensive care unit (Oloffson *et al.*, 1996). All of the studies enrolling general mixed medical-surgical or medical patients enrolled older adults (i.e. they had lower age limits). One of the included studies (Inouye *et al.*, 2007) described a derivation and validation cohort. Associations related to the validation cohort included non-delirious individuals; consequently, only data from the derivation cohort are included. The studies that did not have any age restrictions included those involving patients undergoing elective abdominal aortic aneurysm surgery (Benoit *et al.*, 2005), or surgical and medical patients referred to psychiatric consultation services (Manos and Wu, 1997), and all the studies on cancer or palliative patients (Oloffson *et al.*, 1996; Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Leonard *et al.*, 2008; Sagawa *et al.*, 2009). Given the heterogeneity of study populations and settings, no attempt was made to pool the results of the studies.

Studies also varied in how they defined delirium duration (Table 1), although all looked at presence or absence of delirium at time of discharge or at 2–8 weeks after delirium diagnosis (three studies also included delirium status at 3–6 months after hospital discharge). In some instances, studies also reported recurrence of delirium. As the actual duration of delirium is unknown, for the purposes of this review individuals with recurrent delirium were classified as having "persistent" (instead of "resolved") delirium.

Some studies used categorical measures (e.g. percentage delirious at a pre-specified time point) while others counted the number of delirium days. Some of the studies assessed for delirium until death or discharge (Rudberg *et al.*, 1997; Lawlor *et al.*, 2000; Kelly *et al.*, 2001; Adamis *et al.*, 2006; 2007; Leonard *et al.*, 2008), whereas other studies included only individuals with data at two separate time points or excluded deceased individuals. Fourteen studies defined duration as when delirium resolved according to the DSM or Confusion Assessment Method (CAM; Inouye *et al.*, 1990) criteria, and four studies defined delirium resolution when all delirium symptoms had dissipated (Oloffson *et al.*, 1996; Camus *et al.*, 2000;

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Table 1. Summary of included studies

STUDY AUTHOR	SAMPLE SIZE; POPULATION TYPE (AGE, CLINICAL SERVICE, OTHER)	EXCLUSION CRITERIA, WHEN SPECIFIED (EXCLUDING COMMUNICATION DIFFICULTIES)	DELIRIUM RESOLUTION CRITERIA (TIME ASSESSED)	DECEASED EXCLUDED?	LOSS TO FOLLOW-UP BECAUSE OF DEATH WHEN AVAILABLE OR OTHER CAUSES	ADJUSTED ANALYSIS?[a]	POINT ESTIMATE (PERSISTENCE RATE)
Levkoff *et al.*, 1994	$n = 91$; ≥65 years surgical and medical units	Prevalent delirium	DSM-III criteria (by d/c, after 3 and 6 months)	Yes	N/A[c]	No	At d/c: 58 %[b] At 6 months: 31%
Rudberg *et al.*, 1997	$n = 64$; ≥ 65 years surgical and medical units	If unable to be seen in 48 hrs, or isolated	DSM- IIIR criteria (by d/c or death)	No	Deceased included Other loss to f/u N/A	No	31%[d]
McCusker *et al.* 2003[e]	$n = 193$; ≥ 65 years medical units	Primary CVA, ICU	DSM criteria (by d/c or 8 weeks and 6 months)	Yes	At d/c: 17.3% (death), and 3.3 % (inadequate data) At 6 months: 26% (inadequate data)	No[a]	At d/c: 32% At 6 months: 31%
Adamis *et al.*, 2007	$n = 42$; ≥ 70 years geriatrics	Incident delirium, terminally ill, prior enrollment	CAM criteria (by d/c, death or 28th day)	No	Deceased included Other loss to f/u N/A	Yes	At d/c or death or day 28: 38%
Adamis *et al.*, 2006	$n = 33$; ≥ 70 years geriatrics	Prior study enrollment	CAM criteria (by d/c, death or 28th day)	No	Deceased included Other loss to f/u N/A	No	at d/c or death[d] 72%
Manos and Wu 1997	$n = 94$; surgical and medical units, referred to psychiatry	N/A	DSM-III criteria (by d/c)	Yes	N/A	No	N/A
Koponen *et al.*, 1989	$n = 70$; ≥ 60 years Psychogeriatrics	Alcohol withdrawal	DSM III criteria (by d/c)	Yes	N/A	No	Range days: 3–81
Lawlor *et al.*, 2000	$n = 71$; cancer, palliative unit, on neuroleptics	Other psychiatric diagnoses interfering with delirium assessment	DSM-IV criteria (by d/c or death)	No	Deceased included Other loss to f/u N/A	Yes	At death/ d/c: 44%[f]
Leonard *et al.*, 2008	$n = 121$; palliative unit	Imminent death	DSM-IV criteria (by d/c or death)	No	Deceased included Other loss to f/u N/A	Yes	73%
Edlund *et al.*, 2001	$n = 49$; ≥ 65 years Surgical unit (hip fracture repair)	N/A	DSM-IV criteria on post-op day # 7	Yes	N/A[c]	No	At 1 week: 29%
Benoit *et al.*, 2005	$n = 34$; ≥ 40 years, surgical unit (AAA repair)	Unable to do cognitive tests; visual/ auditory impairment	DSM-IV criteria (at post-op day 6 or d/c)	Yes	N/A	No	At d/c: 0%
Kiely *et al.*, 2004	$n = 85$; ≥ 65 years; post acute care	Terminally ill, residence >25 miles outside research center	CAM criteria (at 28 +/− 3 days)	Yes	5% (death) withdrawal (3%); acute care transfer (6%)[g]	Yes	At 1 month: 51%

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Table 1. Continued.

STUDY AUTHOR	SAMPLE SIZE; POPULATION TYPE (AGE, CLINICAL SERVICE, OTHER)	EXCLUSION CRITERIA, WHEN SPECIFIED (EXCLUDING COMMUNICATION DIFFICULTIES)	DELIRIUM RESOLUTION CRITERIA (TIME ASSESSED)	DECEASED EXCLUDED?	LOSS TO FOLLOW-UP BECAUSE OF DEATH WHEN AVAILABLE OR OTHER CAUSES	ADJUSTED ANALYSIS?[a]	POINT ESTIMATE (PERSISTENCE RATE)
Speciale *et al.*, 2007	$n = 58$; ≥ 65 years, geriatric rehab unit	N/A	CAM criteria (at 1 and at 2 weeks)	Yes	10% (death) 31% for acute care transfer 9% (not specified)	No	Delirium at ≥ 2 weeks: 31%
Kelly *et al.*, 2001	$n = 61$; ≥ 77 years, hospitalized nursing home residents (medical unit)		CAM criteria (by discharge or death)	No[h]	Deceased included Other loss to f/u N/A[h]	No	At death or d/c (72%), or 3 months (25%)[h]
Studies defining resolution by disappearance of all delirium symptoms							
McAvay *et al.*, 2006	$n = 55$; ≥ 70 years, medical unit	NH residents, ICU patients; prevalent delirium	No delirium symptoms (CAM; at d/c)	Yes	N/A[c]	No[a]	At d/c: 44%
Inouye *et al.*, 2007[i]	$n = 106$; ≥ 70 years medical unit	ICU patients; prevalent delirium	No delirium symptoms (CAM; at d/c)	Yes	N/A[c]	No[a]	at d/c: 55%
Oloffson *et al.*, 1996	$n = 90$; cancer, referred to psychiatry		No delirium symptoms (DRS) by 30 days or until death	No[j]	18% (death)	No	10% (at d/c)[j]
Camus *et al.*, 2000	$n = 167$[i]; ≥ 68 years geriatric wards/ referred to psychiatry	Alcohol-related delirium	No delirium (DSM-III) symptoms (by d/c or 3 weeks)	Yes	9% (death)	No	51%[j]
Studies defining delirium resolution by fewer delirium symptoms (using delirium symptom scales):							
Cole *et al.*, 2007[e]	$n = 290$; ≥ 65 years, medical unit	CVA, oncology unit, ICU/CCU	Less symptoms by DI score (at 4 weeks)	Yes	N/A	Yes	4 wks: 78%
Breitbart *et al.*, 2002	$n = 79$; cancer, referred to psychiatry, on Olanzepine	Unable to take post-operative Olanzepine; on other neuroleptics	Better MDAS (≤ 10) score (4–7 days after Olanzepine)	Yes	N/A 4% (incomplete data)	Yes	At 4–7 days: 24%
Sagawa *et al.*, 2009	$n = 100$; cancer, referred to psychiatry	Post-operative, recent intubation, dementia, intracranial disease	DRS ≤ 15 at 1 week	Yes	9 % (death) 2% for moved	Yes	44%

AAA = abdominal aortic aneurysm; age restriction: Y = Yes; N = No; CAM = Confusion Assessment Measure; CCU = critical care unit; CVA = cerebrovascular accident (stroke); d/c = discharge; DI = Delirium Index; DRS = Delirium Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; f/u = follow-up; ICU = intensive care unit; MDAS = Memorial Delirium Assessment Scale; N/A = not available; NH = nursing home; (+) = positive.

[a]Adjusted analysis specifically applies to the outcome of delirium duration (some studies may have applied adjusted analyses for other outcomes, or included non-delirious individuals, but are only listed as providing adjusted analyses if they did this for delirium duration *and* only included delirious individuals).

[b]Includes persistent (27%) and recurrent (31%) delirium; persistence data reported in another publication, Levkoff *et al.*, 1992.

[c]Loss to follow-up rate for death (or other causes) was provided, but included non-delirious individuals (also enrolled in study).

[d]Calculated rate (DSM/CAM positive delirium occurring up to 2 days prior to d/c or death.

[e]These 2 studies overlapped in some included patients, although their definitions for delirium resolution differed.

[f]This refers to the per-patient rate of delirium persistence not the persistence rate per delirious episode (recurrent episodes counted toward non-reversed.

[g]Study also provided refusal rate (25%) and percentage of substitute decision-makers (15%) who could not be contacted.

[h]The persistence rate at 3 months in this study did not include deceased individuals (the persistence rate at discharge did include deceased individuals).

[i]Only used data from validation cohort.

[j]Although patients were assessed until death, they were excluded from persistence data analysis.

McAvay *et al.*, 2006; Inouye *et al*, 2007). Three studies (Breitbart *et al.*, 2002; Cole *et al.*, 2007; Sagawa *et al.*, 2009) defined delirium resolution by improvements in delirium symptom scale scores such as the Delirium Index (DI; McCusker *et al.*, 1998; Cole *et al.*, 2007), the Memorial Delirium Assessment Scale, MDAS (Breitbart *et al.*, 1997; Breitbart *et al.*, 2002) or the Delirium Rating Scale (DRS; Trzepacz *et al.*, 1988; Oloffson *et al.*, 1996; Sagawa *et al.*, 2009).

Overall persistence rates of delirium varied from 0% to 78%. In studies that included data on deceased individuals and used lack of CAM or DSM criteria to define delirium resolution, persistence rates between 31% and 72% were reported. One study involving younger elective abdominal aortic aneurysm patients (Benoit *et al.*, 2005) reported complete resolution of DSM-defined delirium at discharge. Excluding this study, other studies (Edlund *et al.*, 2001; Kiely *et al.*, 2004; Speciale *et al.*, 2007) that used cessation of DSM or CAM criteria to define when delirium had resolved (and excluded deceased individuals) reported persistence rates between 29% and 55% at discharge or at 1–8 weeks after delirium diagnosis. Studies that defined delirium resolution by recovery of all delirium symptoms reported persistence rates between 10% and 55%, and those that defined resolution by fewer delirium symptoms reported persistence rates between 24% and 78%. Two studies assessed delirium persistence six months after diagnosis, by the presence of DSM or CAM criteria, and both found persistence rates around 30% (McCusker *et al.*, 2003; Levkoff *et al.*, 1994). One study reported persistence of DSM-defined delirium in 25% of living individuals three months after hospital discharge (Kelly *et al.*, 2001).

The studies also varied in the dependent variables they assessed. Specific comparator variables that were assessed for their association with delirium duration in at least two studies are summarized in Tables 2–4. Comparator variables could be classified into three broad categories: baseline patient characteristics, characteristics of the delirious state, and the nature of the underlying putative causative factor.

Patient baseline characteristics as determinants of delirium duration

Patient baseline characteristics that were assessed in at least two studies, with regards to their association with delirium duration, included: premorbid dementia or cognitive impairment, presence of any neurodegenerative disease, advanced age, gender, baseline or admission functional dependence, medical comorbidity, education level, history of depression, and visual or hearing impairment (Table 2).

Baseline dementia or cognitive impairment and neurodegenerative disease

Baseline dementia was defined differently across studies. Some studies used dementia scales (Koponen *et al.*, 1989; McCusker *et al.*, 2003; Kiely *et al.*, 2004; Inouye *et al.*, 2007; Cole *et al.*, 2007) such as the Blessed Dementia Scale (Blessed *et al.*, 1968), the Informant Questionnaire of Cognitive Decline in the Elderly (IQCODE; Jorm, 1994), or the DSM criteria; one study (Kelly *et al.*, 2001) used data from the nursing home Minimum Data Set (MDS; Lawton *et al.*, 1998), and some studies relied on whether or not dementia was noted in the medical record (Levkoff *et al.*, 1994; Camus *et al.*, 2000; Breitbart *et al.*, 2002).

Dementia was found to be associated with persistent DSM- or CAM-defined delirium at discharge or up to eight weeks after delirium diagnosis in three studies, in mixed surgical/medical (Levkoff *et al.*, 1994), general medical (McCusker *et al.*, 2003), and post-acute care (Kiely *et al.*, 2004) settings (the latter study found associations in both univariate and multivariate analyses). Two studies found that lack of dementia was associated with complete reversal of all delirium symptoms (Camus *et al.*, 2000; Inouye *et al.*, 2007). Two studies that assessed improvement of delirium symptoms using delirium symptom scales found either an association (Breitbart *et al.*, 2002) or a trend towards slower improvement in dementia (Cole *et al.*, 2007). In one of these studies, involving adult cancer patients of all age ranges treated with Olanzepine (Breitbart *et al.*, 2002), dementia was associated with prolonged delirium symptoms in the bivariate but not the multivariate analysis (which controlled for age). The three studies that did not find a statistically significant association between dementia and prolonged delirium were studies that enrolled psychiatric inpatients, or patients referred to psychiatric consultation services (Koponen *et al.*, 1989; Manos and Wu, 1997) and one study enrolling hospitalized nursing home patients (Kelly *et al.*, 2001); in the latter study, more than 95% of study participants had a prior history of cognitive problems, likely decreasing the power of finding such an association. When provided, based on six studies, strengths of association at discharge (or by eight weeks) between dementia and persistent delirium ranged from an OR of 1.8–8.4. At six months' follow-up, one study found no association between dementia and delirium persistence in a mixed surgical/medical population (Levkoff *et al.*, 1994), although one study in medical inpatients did find an association (McCusker *et al.*, 2003; calculated OR of 6.5 at six months of persistence).

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Table 2. Statistically significant associations between patient characteristics and prolonged delirium duration while in hospital. Multivariate analyses are indicated by (M); all others are univariate (U)

STUDY AUTHOR SAMPLE SIZE; POPULATION	COGNITIVE IMPAIRMENT	NEURO-DEGENERATIVE/ CNS DISEASE[a]	OLDER AGE	FEMALE GENDER	ADL DEPENDENCE	INITIAL FUNCTIONAL STATUS	CO-MORBIDITY (CHARLSON UNLESS OTHERWISE STATED)	INCREASING EDUCATION LEVEL	DEPRESSION	VISUAL IMPAIRMENT	HEAR IMPAIRMENT
General mixed units (surgical and medical)											
Levkoff *et al.*, 1994 N = 91; surgical and medical units	Y, p = 0.03				Y, OR 2.6 (1.2, 5.3)				NS	NS	NS
Rudberg *et al.*, 1997 N = 64; surgical and medical units							Y[b]; p = 0.002				
General medical/geriatric units											
McCusker *et al.*, 2003[c] N = 193; medical unit	Y,[d] p = 0.0001 *OR* 5.1										
Adamis *et al.*, 2007 N = 42; geriatrics			NS	NS (U **and M**);[e]		NS					
Adamis *et al.*, 2006 N = 33; geriatrics			NS								
Referred to psychiatry consult services											
Manos and Wu 1997 N = 49; medical and surgical units, referred to psychiatry	NS[f] p = 0.17										
Koponen *et al.*, 1989 N = 71; pychogeriatrics	NS[f]	NS;									
Cancer/palliative patients:											
Lawlor *et al.*, 2000 N = 71; cancer, palliative unit			NS[g] HRs (U and **M**)								
Leonard *et al.*, 2008 N = 121; palliative unit	NS;		NS				Y[b] ($p < 0.01$; **p (M) = 0.02**				
Surgical patients											
Benoit *et al.*, 2005 N = 33; surgical unit (AAA repair)								Y (-)[h] p = 0.04	Y[i] p = 0.0004		
Other specific patient types											
Speciale *et al.*, 2007 N = 58; geriatric rehab unit			NS p = 0.78	NS p = 0.68 *OR* 1.3		NS p = 0.3	NS p = 0.56				

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Kiely *et al.*, 2004 N = 85; post-acute care	Y[j] U RR 2.7 (1.6, 4.7); **OR (M)** 8.4 (2.4, 29.5)	NS RR 1.3 (0.8, 1.9)	Y: U RR 1.6 (1.1, 2.4) **OR (M)** 4.6 (1.5, 14.6)	NS RR 1.1 (0.7, 1.9)	Y (U) RR 1.6 (1.1, 2.5) **NS (M)**		NS RR 1.0 (0.3, 4.1)	Y RR 1.6 (1.1, 2.4) **NS (M)**	
Kelly *et al.*, 2001 N = 61; hospitalized nursing home residents (medical unit)	NS[k]		NS	NS	NS[k]				
Studies defining resolution by disappearance of all delirium symptoms									
Inouye *et al.*, 2007 N = 106; medical unit	Y[j] OR 3.4 (1.5, 7.8)		NS; OR 1.3 (0.6, 3.0)	NS OR[l] 1.1 (0.5, 2.5)	NS OR 1.8 (0.8, 4.0)		NS; OR 1.5 (0.7, 3.4)	NS; OR 1.0 (0.9, 1.2)	Y; OR 2.4 (1.1, 5.5)
Camus *et al.*, 2000 N = 167; geriatric wards/ referred to psychiatry	Y; p = 0.0002 *OR* 3.3	NS *OR* 0.9	NS	NS; *OR* 0.8			NS[b]		NS[m] NS[m]
Studies that assessed delirium resolution by fewer delirium symptoms (using delirium symptom scales):									
Cole *et al.*, 2007[c] N = 290; medical unit	Trend[dl] OR 1.8 (1.0, 3.3)		Y OR[l] 1.04 (1.0, 1.1)	NS OR 1.3 (0.5, 1.4)[n]			NS[l] OR 0.9 (0.8, 1.1)		
Breitbart *et al.*, 2002 N = 79; cancer, referred to psychiatry, on Olanzepine	Y, p < 0.05 *OR* 3.6 **NS (M): p = 0.4** °		Y, p < 0.001, *OR* 18.3 **Y (M) p = 0.001OR 171.5**	NS p = 0.09		NS p = 0.11			
Sagawa *et al.*, 2009 N = 100; cancer, referred to psychiatry							Y[b] P < 0.001		

AAA = Abdominal Aortic Aneurysm; CNS = Central Nervous System; Y = Yes; N = No; ; Trend = p ≤ 0.1; (+) = positive association.
Odds *OR* = calculated Ratio; OR = provided by study; **Bolded OR (HR or RR) or p-values** represent ORs (HRs, RRs), or p-values from multivariable analysis; NS = not significant.
[a]CNS diseases based on documentation in medical record.
[b]Used number of diagnoses to define co-morbidity.
[c]With overlapping populations (although studies defined delirium resolution differently).
[d]Informant Questionnaire of Cognitive Decline in the Elderly.
[e]Authors did multivariable analysis with gender and IGF-1 and possession of APO ε4, on a sub-sample of the study (n = 17); the multivariable analysis was NS, but the association with gender did approach significance (p = 0.066).
[f]DSM criteria.
[g]Hazard ratios (HR) and confidence intervals for reversibility of delirium provided by authors for older age: univariate HR 0.67 (0.3, 1.2); multivariate **HR** 1.0 (0.4,2.2).
[h]High education associated with shorter delirium.
[i]Measured using Geriatric Depression Scale.
[j]Blessed Scale for dementia.
[k]Used data in Minimum Data Set for nursing homes.
[l]OR of persistence if female (and associated confidence intervals) calculated as 1/OR for persistence if male (as provided in the study); similarly OR for persistence calculated as 1/OR for reversing for risk factors age, Charlson co-morbidity scale, and dementia in Cole *et al.*, 2007.
[m]Visual and hearing impairment were combined in this study and found to not be associated with persistence.
[n]Contacted authors to confirm OR and confidence intervals.
°Multivariate analysis controlled for age, and other variables. Contacted authors who confirmed that in the multivariable analysis, despite being non-significant the direction of association was positive between dementia and delirium irreversibility, despite the OR listed in the study.

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Table 3. Statistically significant associations between delirium characteristics and prolonged delirium duration while in hospital (assessed up to two months after diagnosis). Multivariate analyses are indicated by (M); all others are univariate (U)

STUDY AUTHOR SAMPLE SIZE; POPULATION	PROMINENT HYPOACTIVE (OR LACK OF PROMINENT HYPERACTIVE) SYMPTOMS (MEASURE)	INDIVIDUAL DELIRIUM SYMPTOMS (SXS) (MEASURE)	ONSET: PREVALENT DELIRIUM (VS. INCIDENT)	INCREASED DELIRIUM SEVERITY[a] (MEASURE)	INITIAL COGNITIVE IMPAIRMENT (LOW MMSE)
General mixed units (surgical and medical)					
Rudberg *et al.*, 1997 N = 64; surgical and medical units		NS (DRS)		Y (DRS); p = 0.03	
General medical/geriatric units					
Adamis *et al.*, 2006 N = 33; geriatrics				Y (DRS); p = 0.02	Y; p = 0.003
Adamis *et al.*, 2007 N = 42; geriatrics				NS (DRS)	NS
Referred to psychiatry consult services					
Manos and Wu, 1997 N = 45;[b] surgical and medical units, referred to psychiatry			NS; p = 0.23		
Koponen *et al.*, 1989 N = 71; psychogeriatrics	NS[c]				NS
Cancer/palliative patients					
Lawlor *et al.*, 2000 N = 71; cancer, palliative unit, on neuroleptics			NS; p = 0.17		
Leonard *et al.*, 2008 N = 121; palliative unit		U: NS except trend with disorientation (p = 0.06) and STM impairments (p = 0.1); **M: Y (p = 0.04)** (visuospatial sxs, (DRS)	Y; p < 0.03 *OR* = 2.8	Y; p < 0.001 (DRS)	Y (CTD, (p < 0.001)
Surgical patients					
Edlund *et al.*, 2001 N = 49; surgical unit (hip fracture repair)			Y; p <0.001 *OR* 9.2[d]		

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Other specific patient types				
Kelly *et al.*, 2001 N = 61; hospitalized nursing home residents (medical unit)	Y[c] p < 0.05 *OR* 4.1[e]		Trend, p = 0.10 (MDAS); *OR* 6.7	
Kiely *et al.*, 2004 N = 85; post-acute care			Y (MDAS) RR 2.0 (1.3, 3.1) **OR (M)** 6.2 (1.3, 29.2)	
Speciale *et al.*, 2007 N = 58; geriatric rehab unit				Y; p = 0.03
Studies defining resolution by disappearance of all delirium symptoms				
Inouye *et al.*, 2007 N = 106; medical unit				NS; OR 1.7 (0.7, 3.9)
McAvay *et al.*, 2006, N = 55; medical unit			NS (CAM)	
Oloffson *et al.*, 1996 N = 90; cancer, referred to psychiatry	Y[f] (p < 0.001) *OR* 5.5[g]			
Camus *et al.*, 2000 N = 167; geriatric ward/ referred to psychiatry	NS[h] *OR*[eg] 1.5			
Studies that assessed resolution of delirium symptoms (using delirium symptom scales):				
Cole *et al.*, 2007, N = 290; medical unit	Y OR[i] 1.5 (1.0, 2.3) **OR[i] (M)** 1.6 (1.0, 2.5); (DI)	Disorientation: Trend OR 1.3 (1.0, 1.7); **Y (M), OR[j],** 1.6 (1.1, 2.2) NS for other sxs[k], (DI)		
Breitbart *et al.*, 2002 N = 79; cancer, referred to psychiatray, on Olanzepine	Y, p < 0.006[f] *OR* 5.3 **Y (M); p = 0.01; OR** 11.3 (MDAS)		Y, p = 0.02, *OR* 3.7 (MDAS); **trend (M): p = 0.1; OR** 5.0	

Odds *OR* = calculated Ratio; OR = provided by study; **bolded OR (HR)** or **p-values** represent ORs (HRs), or p-values from multivariable analysis.
CTD = Cognitive Test for Delirium; DRS = Delirium Rating Scale; MDAS = Memorial Delirium Assessment Scale; DI = Delirium Index score; STM = Short Term Memory; CAM = Confusion Assessment Method; Y = Yes; N = No; Trend = p ≤ 0.1; NS = not significant.
[a]Delirium severity was measured: as mean (Rudberg *et al.*, 1997, Adamis *et al.*, 2007), or at the time of initial (Leonard *et al.*, 2008; Breitbart *et al.*, 2002; Kiely *et al.*, 2004; Kelly *et al.*, 2001; McAvay *et al.*, 2006) or second delirium assessments (Adamis *et al.*, 2006).
[b]Only assessed association in medical sub-group.
[c]Used clinical impressions to define hypo-, hyper-, mixed or neither subtypes of delirium.
[d]OR for delirium lasting beyond 1 week.
[e]Compared hypoactive against (hyperactive or mixed).
[f]Compared (hypoactive or neither or mixed) to hyperactive symptoms.
[g]Excluded deceased when OR was calculated.
[h]Used Delirium symptom checklist to derive a score (OR refers to prominent hypoactive symptoms).
[i]OR of recovery if hyperactive symptoms present provided by study.
[j]Analyses controlled for dementia.
[k]The reader is referred to the original study for detailed ORs associated with the various delirium symptoms.

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Table 4. Statistically significant associations between illness characteristics and reversibility of delirium, as assessed up to 2 months after onset (all univariate, U, unless specifically stated as multivariate, M)

		ASSOCIATED ACUTE CONDITIONS:[a]														
STUDY AUTHOR, SAMPLE SIZE, POPULATION	ILLNESS SEVERITY (APACHE)/APS	HYPOXIA	ADVERSE DRUG REACTION/ POLYPHARMACY/ PSYCHOTROPIC DRUG USE	DEHYDRATION	METABOLIC/ ENDOCRINE/ ELECTROLYTEABNORMALITY	INFECTION	FEBRILE ILLNESS/ HYPER-THERMIA	CNS SPREAD	SEIZURE	STROKE (CEREBROVASCULAR ACCIDENT)	HEAD TRAUMA	SURGICAL DELIRIUM (VS. MEDICAL)	LOW ALBUMIN	HIGH C-REACTIVE PROTEIN / INFLAMMATION
General mixed units (surgical and medical)														
Levkoff *et al.*, 1994[b] N = 91; surgical and medical units					NS	NS (symptomatic infection);	NS (>99 F)		NS	NS	NS	NS		NS
Rudberg *et al.*, 1997 N = 64; surgical and medical units			Trend (+) p = 0.07											
General medical/geriatric units														
Adamis *et al.*, 2006 N = 33; geriatrics	NS													
Adamis *et al.*, 2007 N = 42; geriatrics	NS				NS								NS	NS

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Referred to psychiatry consult services											
Manos and Wu, 1997 N = 94; surgical and medical units, referred to psychiatry									Y (+) P = 0.004[c]		
Cancer /palliative patients											
Leonard *et al.*, 2008 N = 121; palliative unit		NS		NS	NS		NS	NS NS	NS		
Lawlor *et al.*, 2000 N = 71;[b] cancer, palliative unit, on neuroleptics	Y; HR 0.4 (0.2, 0.8) **HR (M)** 0.3 (0.1, 0.7)	Y HR 8.9 (2.1, 36.7) **HR (M)** 6.7 (1.5, 29.6)	Y HR 2.3 (1.2, 4.6) **NS HR (M)** 1.5 (0.7, 3.2)	Y HR 0.4 (0.2, 0.9); **HR (M)-Trend** 0.5 (0.2, 1.0)	NS HR 0.6, (0.3, 1.2) **Y HR (M)** 0.2 (0.1, 0.6)		NS; P = 0.10				
Surgical patients											
Benoit *et al.*, 2005 N = 34; surgical unit (AAA repair)		Y; p = 0.04									
Other patient types											
Speciale *et al.*, 2007 N = 58; geriatric rehab unit										NS; p = 0.9	NS P = 0.9
Kelly *et al.*, 2001 N = 61; hospitalized nursing home residents (medical unit)	NS										

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Table 4. Continued.

	ASSOCIATED ACUTE CONDITIONS:[a]														
STUDY AUTHOR, SAMPLE SIZE, POPULATION	ILLNESS SEVERITY (APACHE)/APS	HYPOXIA	ADVERSE DRUG REACTION/ POLYPHARMACY/ PSYCHOTROPIC DRUG USE	DEHYDRATION	METABOLIC/ ENDOCRINE/ ELECTROLYTEABNORMALITY	INFECTION	FEBRILE ILLNESS/ HYPER-THERMIA	CNS SPREAD	SEIZURE	STROKE (CEREBROVASCULAR ACCIDENT)	HEAD TRAUMA	SURGICAL DELIRIUM (VS. MEDICAL)	LOW ALBUMIN	HIGH C-REACTIVE PROTEIN / INFLAMMATION
Studies defining resolution by disappearance of all delirium symptoms														
Inouye *et al.*, 2007[b] N = 106; medical unit	NS[d]; OR 0.8 (0.3, 1.7)		NS[d] OR 1.7 (0.8, 5.0) OR 2 (0.9, 5.0)	Y[d] OR 0.5 (0.2, 1.0)									NS[d] OR 1.1 (0.5, 2.5)	
McAvay *et al.*, 2006[b] N = 55; medical unit	Y P < 0.05													
Camus *et al.*, 2000[b] N = 167; geriatric ward, referred to psychiatry			NS *OR* 1.3		Y; p < 0.0001 *OR* 5.4		Y; p = 0.003; *OR* 4.5					NS *OR* 0.4		
Studies that assessed resolution of delirium symptoms (using delirium symptom scales):														
Cole *et al.*, 2007 N = 290; medical unit	NS OR 1.0 (0.9, 1.1)													

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Breitbart *et al.*, 2002 N = 79; cancer, referred to psychiatry, on Olanzepine referred	Y[d] p < 0.05, *OR* 0.3 **Trend (M) p = 0.09 OR 0.2**	NS (opioids p = 0.6; steroids p = 0.2; side effects from Olanzepine, p = 0.4)	NS p = 0.5		NS P = 0.4	Y[d] p < 0.04; OR 0.2; **Y (M) p = 0.005; OR (M)** 0.01	
Sagawa *et al.*, 2009[b] N = 100; cancer, referred to psychiatry	NS OR 0.4 (0.1, 2.0)[e]	Opiods OR 0.4 (0.2, 0.9) **NS in M[f]** Bdzs OR 1.1 (0.4, 3.0) Steroids OR 1.1 (0.3, 3.3)	NS OR 0.7 (0.3, 1.8)	NS OR 0.5 (0.2, 1.2)[e]			NS OR 0.5 (0.2, 1.1)

OR = calculated odds ratio; OR = provided by study; **bolded OR (HR)** or **p-values** represent ORs (HRs), or p-values from multivariable analysis.
[a] Often not defined in studies except occasionally; specific definitions for studies, when provided follow below.
[b] Temporal association was stipulated in establishing causation, or only incident cases of delirium were enrolled.
Y = Yes; N = No; Trend: $p \leq 0.1$; (+) = positive association; (−) = negative association (means that with the condition there was slower resolution of delirium); NS = not significant; APS = acute physiology score (Knaus *et al.*, 1985).
[c] Used survival (of delirium) curve to calculate p-value.
[d] Study provided OR of having prolonged delirium with risk factor- to convert this to association with reversibility 1/OR (for prolonged delirium) was used.
[e] <10% of sample had hypoxia/ hypercalcemia.
[f] Multivariable analysis controlled for performance status, clinical stage of cancer, age and gender.

Study definitions where provided:
(1) Hypoxia: Lawlor *et al.*, 2000 and Sagawa *et al.*, 2009: oximetry <90% on room air or requiring oxygen (2 l) to maintain saturation ≥90%
(2) Adverse drug reactions/ polypharmacy/ psychotropic drug use: Breitbart *et al.*, 2002: opiods, steroids, or side effects to Olanzepine; Lawlor *et al.*, 2000: opioids and non-opioids (methylphenidate, methotrimeprazine, anticholinergic drugs, SSRIs, theophylline, tricyclic antidepressants, haloperidol, benzodiazepines); Sagawa *et al.*, 2009 assessed opioids, benzodiazepines (bdzs) and steroid side effects; Leonard study: frequency of prescription of: antipsychotics, antidepresssants, psychostimulants, steroids, opioids and benzodiazepines; Inouye *et al.*: ≥3 new drugs (psychotropic OR = 2 (95% CI: 0.9, 5.0), or general drugs OR = 1.7 (95% CI: 0.8, 5.0)) in one day prior to delirium; Benoit *et al.*, 2005: general psychotropic drug use not otherwise specified prior to surgery; Rudberg *et al.*, 1997: polypharmacy defined by: average number of medications, or prescribed drugs.
(3) Dehydration: Inouye *et al.*, 2007: elevated BUN/Creatinine ratio; Lawlor *et al.*, 2000: Increased Creatinine (>115μmol/l) and BUN (>8 mmol/l) without GI bleed, or Increased BUN (>8 mmol/l) or Creatinine (>115 μmol/l) which responds to hydration (returning to reference range or a 30% decrease) OR hyper (>150 mmol/l) / hypo (<130 mmol/l)- natremia responsive to hydration (returning to reference range or >130 mmol/l).
Sagawa *et al.*, 2009: Creatinine >1.3 or urea nitrogen level >20 mg/dl (in absence of gastrointestinal bleeding with hydration) or sodium >150 mmol/l or <130 mmol/l.
(4) Metabolic/ endocrine/ electrolyte abnormalities: Lawlor *et al.*, 2000: persistent creatinine elevation (>150 μmol/l) or hypoglycemia (glucose <4 mmol.l), or hypomagnesemia (Mg <0.7 mmol/l), or aspartate transaminase >40 U/l or alanaine aminotransferase >50 U/l or bilirubin >20, 000 μmol/l, or corrected calcium >2.6 mmol/l; Levkoff *et al.*, 1994: hyponatremia/ hypernatremia, and hypo or hyperglycemia; Sagawa et al.: any of: aspartate aminotranferase >40 U/l, alanine aminotransferase >50 U/l, bilirubin >1.1 mg/dl, persistent Creatinine >1.7 mg/dl, glucose <72 mg/dl; Sagawa also assessed calcium (corrected for albumin) >10.4 mg/dl (NS): OR = 0.5, (0.3, 3.0); Adamis *et al.*, 2007: calcium level.
(5) Infection: Lawlor *et al.*, 2000*:* non-respiratory infection.
(6) Inflammation or high CRP: high CRP: Speciale *et al.*, 2007; Adamis *et al.*, 2007; abnormal WBC: Levkoff *et al.*, 1994; high WBC or high CRP (>0.4 mg/dl): Sagawa, *et al.* 2009.
(7) CNS spread/Intracranial factor: Lawlor *et al.*, 2000: improvement in delirium within 5 days of initiating steroid treatment or within 4 weeks of radiotherapy or chemotherapy for brain tumor.

The presence of any neurodegenerative disease as determined from the medical record (e.g. stroke, disease of the central nervous system not otherwise specified, or Parkinson's disease) was not associated with persistent delirium at discharge (or by 3–4 weeks) in three studies in psychiatric or geriatric (Camus *et al.*, 2000; Koponen *et al.*, 1989) or post-acute care patients (Kiely *et al.*, 2004).

Age, gender and education level

Age was not associated with prolonged delirium in seven studies (Camus *et al.*, 2000; Lawlor *et al.*, 2000; Kelly *et al.*, 2001; Adamis *et al.*, 2006; 2007; Inouye et al., 2007; Speciale *et al.*, 2007). However, one study suggested an association between older age and persistent CAM-defined delirium in both uni- and multivariate analyses (Kiely *et al.*, 2004). Two studies showed an association between older age and persistent delirium symptoms on delirium scales in older medical inpatients (Cole *et al.*, 2007) and in cancer patients (Breitbart *et al.*, 2002). The latter study did not have any age restriction in participants and showed a very large association in the multivariate analysis. Based on five studies, a wide range of strengths of association (HRs or ORs) were seen from 1 to 171. Gender did not affect delirium duration. (Camus *et al.*, 2000; Kelly *et al.*, 2001; Kiely *et al.*, 2004; Breitbart *et al.*, 2002; Adamis *et al.*, 2007; Cole *et al.*, 2007; Inouye *et al.*, 2007; Speciale *et al.*, 2007). ORs across five studies between female gender and persistence ranged from 0.8 to 1.3. Educational level and delirium duration were inversely associated in one study (Benoit *et al.*, 2005) in patients undergoing abdominal aortic aneurysm repair, and positively associated in another study (in bivariate but not in multivariate analyses; Kiely *et al.*, 2004), or not associated with each other (in medical patients; Inouye *et al.*, 2007).

Other factors

The association between functional dependence and delirium duration varied across studies. Some studies assessed the association of pre-hospital functional dependence (assessed through caregiver-based questionnaires), whereas others measured initial functional status on individuals at study enrollment. These were differentiated because the latter measured functional status when already delirious and may differ from baseline, pre-hospital functional ability. In one study (Adamis *et al.*, 2006), it was not clear when functional status was assessed. Three studies (Breitbart *et al.*, 2002; Adamis *et al.*, 2007; Speciale *et al.*, 2007), which measured functional status at the time of enrollment into the study, using the Barthel scale (Mahoney and Barthel, 1965) in an aging and rehabilitation ward (Speciale *et al.*, 2007) and in an acute geriatric ward (Adamis *et al.*, 2007) or the Karnofsky scale (in cancer patients; Breitbart *et al.*, 2002), did not find initial functional status to be associated with either longer duration of CAM-defined delirium or delirium symptoms (latter measured in Breitbart *et al.*, 2002) during hospitalization.

In the studies that assessed pre-hospital functional status, two studies, one in mixed surgical/medical patients (Levkoff *et al.*, 1994) and the other in the post-acute care setting (Kiely *et al.*, 2004), found an association between ADL-dependence and persistent CAM- or DSM-defined delirium. Two studies, one conducted in a medical population (Inouye *et al.*, 2007; assessed for complete resolution of delirium symptoms) and the other in a nursing home population (Kelly *et al.*, 2001) did not find such an association. In the latter study, functional information, elicited through the nursing home MDS database, revealed that all participants were dependent for at least one ADL so the effect of functional dependence on delirium duration may have been difficult to assess. In one of the positive studies (Kiely *et al.*, 2004), baseline functional dependence was not associated with increased delirium duration in multivariate analyses. The strengths of association between pre-hospital functional dependence and persistent delirium from three studies ranged from 1.8 to 2.6 (2 ORs and 1 RR).

Comorbidity measured using the Charlson scale (Charlson *et al.*, 1987) was not associated with persistent delirium (Kiely *et al.*, 2004; Inouye *et al.*, 2007; Speciale *et al.*, 2007; Cole *et al.*, 2007). However, three out of four studies suggested that increasing numbers of diagnoses are associated with increased delirium duration in the mixed medical/surgical (Rudberg *et al.*, 1997) and palliative or cancer populations (Leonard *et al.*, 2008; Sagawa *et al.*, 2009); one study did not find an association between increasing medical diagnoses and delirium symptom resolution (Camus *et al.*, 2000).

Depression was either positively (Benoit *et al.*, 2005) associated with longer delirium or not (Levkoff *et al.*, 1994). Visual impairment was associated with longer delirium in hospital in one study (Inouye *et al.*, 2007) but not in two others (Levkoff *et al.*, 1994; Camus *et al.*, 2000). Information on visual impairment in the latter two studies was elicited from the patient's chart. Chart-elicited hearing impairment was not associated with persistent delirium at discharge (Levkoff *et al.*, 1994; Camus *et al.*, 2000).

Specific characteristics of the delirious state as predictors of delirium duration

The delirious state was characterized in some studies by the delirium sub-type (hypoactive,

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hyperactive, mixed or neither), the presence of other specific delirium symptoms, delirium severity (measured with severity scales), delirium onset (whether prevalent or incident), and the extent of initial cognitive impairment (see Table 3).

Similar to findings of a prior review (de Rooji *et al.*, 2005), we found that studies often defined delirium subtypes (hypoactive, hyperactive, mixed or neither) differently. Some used DSM-validated scales such as the Delirium Rating Scale (DRS; Trzepacz *et al.*, 1988), the Memorial Delirium Assessment Scale (MDAS; Breitbart *et al.*, 1997) or the Delirium Index (DI; McCusker *et al.*, 1998) to measure hypoactive or hyperactive symptoms. One study used a delirium symptom checklist to derive a mean score of hypoactive or hyperactive symptoms to categorize delirium subtype (Camus *et al.*, 2000) while other studies used clinical judgment to define subtypes (Koponen *et al.*, 1989; Oloffson *et al.*, 1996; Kelly *et al.*, 2001). Nonetheless, four out of six studies found hypoactive (or lack of hyperactive) symptoms to be associated with persistent delirium symptoms in medical (Cole *et al.*, 2007), cancer (Oloffson *et al.*, 1996; Breitbart *et al.*, 2002) or nursing home residents (Kelly *et al.*, 2001), at discharge or at one month after delirium diagnosis. There were two studies that did not find an association between CAM- or DSM-defined persistent delirium and hypoactive symptoms; one was conducted in a psychiatry unit (Koponen *et al.*, 1989), and the other included patients both from a geriatric unit and those referred to psychiatry (Camus *et al.*, 2000). Based on five studies, the OR of persistence in the presence of hypoactive symptoms (or the absence of hyperactivity) ranged from 1.5 to 11.3. The three studies (Rudberg *et al.*, 1997; Cole *et al.*, 2007; Leonard *et al.*, 2008) that assessed the presence of disorientation, perceptual disturbances, or other specific delirium symptoms using DSM-derived scales did not find consistent associations between specific delirium symptoms and persistent delirium, or delirium symptoms.

Out of eight studies that measured delirium severity, five found an association between increased delirium severity and prolonged DSM- or CAM-defined delirium (Rudberg *et al.*, 1997; Kiely *et al.*, 2004; Adamis *et al.*, 2006; Leonard *et al.*, 2008) or delirium symptoms (Breitbart *et al.*, 2002). Two of these studies conducted multivariate analyses and measured severity with the MDAS (Breitbart *et al.*, 2002; Kiely *et al.*, 2004); in one of these studies (Kiely *et al.*, 2004), both bivariate and multivariate analyses yielded an association with prolonged (defined by CAM criteria) delirium, whereas the other study found a trend for an association with persistent delirium symptoms in the multivariate analysis (Breitbart *et al.*, 2002). Three studies out of four (Rudberg *et al.*, 1997; Adamis *et al.*, 2006; 2007; Leonard *et al.*, 2008) that used the DRS (Trzepacz *et al.*, 1988) found bivariate associations between increased severity and delirium duration. One study on nursing home patients found a trend towards increased MDAS severity scores and delirium duration (Kelly *et al.*, 2001). One negative study (McAvay *et al.*, 2006) used an alternate method (neither the MDAS, not the DRS) to measure severity. Most studies measured delirium severity early in the course of delirium, although two studies did use the mean of delirium severity scores (Rudberg *et al.*, 1997; Adamis *et al.*, 2007). Based on three studies, the OR of persistence with more severe delirium, measured with the MDAS ranged from 5.0 to 6.7.

Prevalent delirium was associated with longer lasting delirium in a study of delirious hip fracture (Edlund *et al.*, 2001) and palliative patients (Leonard *et al.*, 2008) but not in two other studies involving referred medical/surgical (Manos and Wu, 1997) or cancer patients (Lawlor *et al.*, 2000).

A lower initial level of cognitive impairment, as assessed by the score on the Mini-mental State Examination (MMSE) (measured while delirious in hospital) or measured with the Cognitive Test in Delirium (Hart *et al.*, 1996) was associated with longer delirium in three studies, conducted in geriatric care units (Adamis *et al.*, 2006), rehabilitation care units (Speciale *et al.*, 2007) and palliative care units (Leonard *et al.*, 2008), but this was not confirmed in three other studies among medical or geriatric inpatients (Inouye *et al.*, 2007; Adamis *et al.*, 2007) or in patients referred for psychiatric consultation (Koponen *et al.*, 1989).

Underlying disease effects on delirium duration

Delirium is a non-specific symptom complex associated with multiple illnesses. As a consequence of the non-specific nature of delirium, elucidating the exact underlying contributory cause(s) can be difficult. Most of the studies that looked at the effect of the putative underlying acute illnesses used diagnoses listed in medical records, although they did not always specify how the acute illnesses were defined (see Table 4). In some cases, studies specifically stipulated the need for a temporal relation between the underlying acute condition and occurrence of delirium, or they enrolled individuals only with incident delirium, who may have had the associated illness prior to or concurrently with delirium onset (Levkoff *et al.*, 1994; Camus *et al.*, 2000; Lawlor *et al.*, 2000; McAvay *et al.*, 2006; Inouye *et al.*, 2007; Sagawa *et al.*, 2009).

In general, the studies by Adamis *et al.* (2006; 2007), Cole *et al.* (2007), Inouye *et al.* (2007) and

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Kelly *et al.* (2001) found that severity of illness measured with the APACHE or APS scale (Knaus *et al.*, 1985) did not affect the rate of resolution of delirium, although one study (McAvay *et al.*, 2006) suggested that higher APACHE scores are associated with faster resolution of delirium.

Hypoxic conditions were associated, in bivariate analyses, with lack of resolution of delirium or delirium symptoms in two studies involving cancer patients (Lawlor *et al.*, 2000; Breitbart *et al.*, 2002;); multivariate analyses either confirmed an association (Lawlor *et al.*, 2000) or a trend toward an association (Breitbart *et al.*, 2002, $p = 0.09$) between persistent delirium (or delirium symptoms) and hypoxia. However this was not confirmed in another study (Sagawa *et al.*, 2009) of cancer patients, although fewer than 10% of individuals had hypoxic conditions in the latter study. ORs or HRs of delirium resolution in these three studies for hypoxic conditions ranged from 0.2 to 0.4.

There was little evidence for an association between delirium duration and infectious causes (Levkoff *et al.*, 1994; Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Leonard *et al.*, 2008), abnormal serum albumin levels (Adamis *et al.*, 2007; Inouye *et al.*, 2007; Speciale *et al.*, 2007), seizure (Levkoff *et al.*, 1994; Leonard *et al.*, 2008), cerebrovascular accident (Levkoff *et al.*, 1994; Leonard *et al.*, 2008) or head trauma (Levkoff *et al.*, 1994; Leonard *et al.*, 2008). There was also little evidence for an association with high C-reactive protein (Adamis *et al.*, 2007; Speciale *et al.*, 2007) or inflammation as measured by high white blood cell count (Levkoff *et al.*, 1994; Sagawa *et al.*, 2009).

There were less consistent findings for other putative causes for delirium, such as adverse drug reactions. Drug causes were defined differently across studies with some studies looking at general or psychotropic drugs not otherwise specified (Rudberg *et al.*, 1997; Camus *et al.*, 2000; Inouye *et al.*, 2007), whereas other studies specifically assessed certain drug types such as neuroleptics, narcotics, benzodiazepines and steroids (Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Leonard *et al.*, 2008; Sagawa *et al.*, 2009). Some studies looked at numbers of drugs (Rudberg *et al.*, 1997) or the number of new drugs prescribed prior to delirium onset (Inouye *et al.*, 2007). Results of studies assessing associations between drug causes of delirium and delirium duration were quite variable, with some reporting an association with slower (Benoit *et al.*, 2005) or faster resolving delirium (Lawlor *et al.*, 2000), or a trend towards this (Rudberg *et al.*, 1997), and others reporting no association (Camus *et al.*, 2000; Breitbart *et al.*, 2002; Inouye *et al.*, 2007; Leonard *et al.*, 2008; Sagawa *et al.*, 2009). There were also inconsistent findings from studies that assessed whether delirium duration differed when there was CNS involvement from cancer (Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Leonard *et al.*, 2008), dehydration (Lawlor *et al.*, 2000; Breitbart *et al.*, 2002; Inouye *et al.*, 2007; Sagawa *et al.*, 2009), and metabolic, endocrine or electrolyte disorders (Levkoff *et al.*, 1994; Camus *et al.*, 2000; Lawlor *et al.*, 2000; Adamis *et al.*, 2007; Leonard *et al.*, 2008; Sagawa *et al.*, 2009). Studies also often differed in how these entities were defined.

Discussion

Systematic reviews of delirium are hampered by the heterogeneity of delirium. Multiple causative factors have been linked to delirium, thereby making it a non-specific syndrome (Lipowski, 1987; Rockwood, 1989) which can be experienced by very different patient populations, have highly variable natural histories (Rudberg *et al.*, 1997) and be associated with multiple adverse outcomes. Nonetheless, efforts to summarize what is known about various aspects of delirium are important to guide future studies and improve our understanding of delirium.

We systematically reviewed the literature to assess what is known about factors impacting on delirium duration or persistence. Persistent delirium has been associated with functional limitations and death (Marcantonio *et al.*, 2000; McCusker *et al.*, 2003; Speciale *et al.*, 2007; Kiely *et al.*, 2009; Cole *et al.*, 2009), thus suggesting that delirium duration is an important outcome. Results must, however, be interpreted with caution. Many of the reported findings represent *post hoc* analyses of larger delirium studies, which had other primary study objectives, with small sample sizes, and many did not control for confounding factors or report confidence intervals. As such, results should be regarded as strictly hypothesis generating rather than providing answers. The studies also varied in the populations they enrolled, their interventions or management protocols, how they defined when delirium had resolved and their comparator variables, thereby making pooling difficult.

We limited the follow-up to a relatively short period (up to six months after delirium onset). Although the expected duration of delirium is unknown, it was felt that given the baseline vulnerability of delirious individuals (Inouye and Charpentier, 1996), these individuals would be at risk of suffering from other intercurrent illnesses (Maracantonio *et al.*, 2005), with longer time periods of observation, which could introduce even greater heterogeneity into the review findings.

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Similar to what has been reported in a recent systematic review (Cole *et al.*, 2009), studies in this review support the fact that persistence of delirium at discharge or at one to eight weeks after diagnosis is common, regardless of which definition is used for delirium resolution, ranging from 0% in one study of elective abdominal aortic aneurysm patients to 10–78% in other inpatient populations. Generally higher rates were observed when deceased individuals were included. When DSM or CAM criteria were used to define when delirium ends, persistence rates were found in survivors of around 30% at six months after diagnosis.

Dementia was found in many studies to increase the duration of delirium across diverse clinical settings. This was not always observed in studies of patients referred to psychiatry consultation services, or the hospitalized nursing home population, possibly reflecting a referral bias and the predominance of dementia in the nursing home population. In one study of adult cancer patients (not restricted to the elderly population), dementia was not found to be associated with persistence in multivariate analyses when factors such as age were controlled for. This may reflect the well-established association between dementia and older age, possibly causing collinearity in multivariate analyses. Although we did not pool results, ORs between dementia and delirium persistence ranged from slightly more than 1 to 8 or more. Advanced age was associated in some studies, although not all, with prolonged delirium, but strengths of association varied greatly across studies. Pre-hospital functional dependence may also herald someone at risk of having sustained delirium symptoms, although not all studies confirmed this. Functional status, measured while already delirious in hospital, was not associated with the length of the delirious episode. Comorbidity, measured with the Charlson Index, and gender did not correlate with length of a delirious episode, although when comorbidity was measured with diagnostic counts it was often found to be associated with longer delirium.

Our review also suggests that aspects of the symptomatology of the delirious state may be helpful prognostically. Increasing delirium severity, measured with scales such as the Memorial Delirium Assessment Scale or the Delirium Rating Scale, was also associated with increased duration of the delirium (ORs in the 5–7 range). Despite the differences in how delirium subtypes were defined across studies, hypoactive symptoms were also suggested in some to indicate a propensity for longer lasting delirium (ORs ranging from slightly more than 1 to 11 or more).

In spite of the inherent difficulties in establishing what acute illness may be contributing to delirium, most studies suggested that severity of illness had little impact on delirium duration but that hypoxic conditions, at least in the cancer population, were associated with prolonged delirium (ORs or HRs of reversing in the 0.2–0.4 range). Differences in how studies defined other causative factors may partially contribute to differences found across studies when looking at other variables.

Findings from our review are consistent with the possibility that delirium in a demented individual may have a different natural history, possibly lasting longer, than delirium in a cognitively intact individual. However, studies have also suggested that dementia in a delirious individual is not associated with (Kelly *et al.*, 2001; Andrew *et al.*, 2005) and may even be protective against (McCusker *et al.*, 2002; Pitkälä *et al.*, 2005; Kiely *et al.*, 2007) increased mortality compared to non-demented delirious individuals. This may reflect the ease with which a demented individual becomes delirious, regardless of the noxiousness of the inciting insult (the noxiousness of the insult may directly impact on mortality); conversely, it may take longer for the full delirium syndrome in a demented individual to dissipate.

Our review also suggests that measuring delirium severity may assist in determining whether a delirious episode is likely to persist at least until discharge. Other studies have suggested that increasing delirium severity is also associated with increased mortality (Kelly *et al.*, 2001; 2007; McCusker *et al.*, 2002). Taken together, this suggests that a measure of delirium severity may assist in prognostication, and should routinely be checked when delirium is diagnosed. This also supports the APA's Practice Guidelines on delirium (American Psychiatric Association, 1999).

Hypoxia in cancer patients was associated with prolonged delirium duration in two out of three studies (the negative study had few hypoxic individuals, but showed a similar strength of association). Another study, not included in this review, reported that decreased oxygen saturation in delirious cancer patients was associated with increased 30-day mortality, compared to delirious cancer patients with normal oxygen saturation (Tuma and DeAngelis, 2000). In two other previously published studies of delirious inpatients, correction of hypoxemia (as opposed to correction of other acute illnesses) was not always associated with improvement of delirium (Rockwood, 1989) in the medical setting and cancer setting (Morita *et al.*, 2001). All of these are consistent with the possibility that hypoxia itself carries a poorer prognosis, or that, alternatively, the delirious brain may be particularly

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susceptible to further irreversible damage from hypoxia. This deserves further study as it may offer insights into mechanisms of poor recovery after delirium.

Further research is needed to elucidate the role of certain variables or characteristics in predicting poor recovery from delirium in older hospitalized medically ill adults. Such information can be used to develop and validate a prognostic model to predict poor recovery after the occurrence of delirium. This may enable clinicians to make evidenced-based management decisions and guide future interventional research aimed at decreasing adverse outcomes associated with delirium.

Study limitations

This study should be viewed as strictly hypothesis-generating. All of the included studies were observational and some had small sample sizes. Included studies were required to meet certain methodological criteria in order to be included such as the use of a valid definition of the two groups (persistent or resolved delirium), consecutive enrollment (to limit selection bias), and the requirement of some reporting of statistical significance. However, delirium duration was often not the primary outcome of interest but rather a secondary outcome or a post-hoc analysis, and most of the included studies did not adjust for confounders or use multivariate analyses when assessing variables associated with delirium persistence. If we had restricted our review to include only those studies that reported adjusted results we would not have had enough studies to derive hypothesis-generating questions. Instead, we chose to highlight the studies that did use multivariable or adjusted analyses so that readers would be aware of when adjusted analyses were done. Adjusted analyses, although generally preferred, can have some limitations, including collinearity, and are more likely to be under-powered to detect subtle associations (compared to bivariate analyses). Another potential drawback stems from the inclusion of so many different patient populations. Although this does increase generalizibility, it may also make the studies too heterogeneous for conclusions to be drawn safely from them. No attempt was therefore made to pool results.

Conclusions

Our review provides a first essential step to understanding the heterogeneity of delirium by assessing what is known broadly about determinants of delirium persistence. Findings should be viewed as hypothesis-generating. Results suggest that there may be some variables, including patient baseline characteristics (dementia, number of comorbid conditions), characteristics of the delirious state (the hypoactive subtype and increasing delirium severity) and the underlying acute illness (hypoxia), which may have prognostic significance. Results from this review should help to guide future studies around management and prognosis of this common and devastating condition.

Conflict of interest

None.

Description of authors' roles

Monidipa Dasgupta was responsible for study concept and design. Both Mondipa Dasgupta and Loretta M. Hillier were responsible for the literature searches, quantitative data extraction and analysis and manuscript preparation.

References

Adamis, D., Treloar, A., Martin, F. and MacDonald, A. J. D. (2006). Recovery and outcome of delirium in elderly medical inpatients. *Archives of Gerontology and Geriatrics*, 43, 289–298.

Adamis, D., Treloar, A., Martin, F., Gregson, N., Hamilton, G. and MacDonald, A. J. D. (2007). APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. *International Journal of Geriatric Psychiatry*, 22, 688–694.

American Psychiatric Association (1987). *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edn. Washington, DC: American Psychiatric Association.

American Psychiatric Association (1994). *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. Washington, DC: American Psychiatric Association.

American Psychiatric Association (1999). Practice guidelines for the treatment of patients with delirium. *American Journal of Psychiatry*, 156 (Suppl. 5), 1–20.

Andrew, M. K., Freter, S. H. and Rockwood, K. (2005). Incomplete functional recovery after delirium in elderly people: a prospective cohort study. *BMC Geriatrics*, 5, 5.

Benoit, A. G. *et al.* (2005). Risk factors and pervalence of perioperative cognitive dysfunction in abdominal aneurysm patients. *Journal of Vascular Surgery*, 42, 884–890.

Blessed, G., Tomlinson, B. E. and Roth, M. (1968). The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, 114, 797–811.

Breitbart, W., Rosenfeld, B., Roth, A., Smith, M. J., Cohen, K. and Passik, S. (1997). The Memorial Delirium Assessment Scale. *Journal of Pain and Symptom Management*, 13, 128–137.

https://doi.org/10.1017/S1041610209991517 Published online by Cambridge University Press

Breitbart, W., Tremblay, A. and Gibson, C. (2002). An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients. *Psychosomatics*, 43, 175–182.

Camus, V., Gonthier, R., Dubos, G., Schwed, P. and Simeone, I. (2000). Etiologic and outcome profiles in hypoactive and hyperactive subtypes of delirium. *Journal of Geriatric Psychiatry and Neurology*, 13, 38–42.

Charlson, M. E., Pompei, P., Ales, K. L. and MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *Journal of Chronic Diseases*, 40, 373–383.

Cole, M., McCusker, J., Ciampi, A. and Dyachenko, A. (2007). An exploratory study of diagnostic criteria for delirium in older medical inpatients. *Journal of Neuropsychiatry and Clinical Neurosciences*, 19, 151–156.

Cole, M. G., Ciampi, A., Belzile, E and Zhong, L. (2009). Persistent delirium in older hospital patients: a systematic review of frequency and prognosis, *Age and Ageing*, 38, 9–26.

de Rooij, S. E., Schuurmans, M. J., van der Mast, R. C. and Levi, M. (2005). Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *International Journal of Geriatric Psychiatry*, 20, 609–615.

Edlund, A., Lundström, M., Brännström, B., Bucht, G. and Gustafson, Y. (2001). Delirium before and after operation for femoral neck fracture. *Journal of the American Geriatrics Society*, 49, 1335–1340.

Elie, M., Cole, M. G., Primeau, F. J. and Bellavance, F. (1998). Delirium risk factors in elderly hospitalized patients. *Journal of General Internal Medicine*, 13, 204–212.

Francis, J. and Kapoor, W. N. (1992). Prognosis after hospital discharge of older patients with delirium. *Journal of the American Geriatrics Society*, 40, 601–606.

Guyatt, G., Drummond, R., Meade, M. O., and Cook, D. J. (2002). *Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice*. Chicago: AMA Press.

Hart, R. P., Levenson, J. L., Sessler, C. N., Best, A. M., Schwartz, S. M. and Rutherford, L. E. (1996). Validation of a cognitive test for delirium in medical ICU patients. *Psychosomatics*, 37, 533–546.

Inouye, S. K. (2006). Delirium in older persons. *New England Journal of Medicine*, 354, 1157–1165.

Inouye, S. K. and Charpentier, P. A. (1996). Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*, 275, 852–857

Inouye, S. K., van Dyck, C. H, Alessi, C. A., Balkin, S., Siegal, A. P. and Horwitz, R. I. (1990). Clarifying confusion: the Confusion Assessment Method. *Annals of Internal Medicine*, 113, 941–948.

Inouye, S. K., Zhang, Y., Jones, R., Kiely, D. K., Yang, F. and Marcantonio, E. R. (2007). Risk factors for delirium at discharge. *Archives of Internal Medicine*, 167, 1406–1413.

Jorm, A. F. (1994). A short form of the informant questionnaire on cognitive decline in the elderly (IQCODE): development and cross-validation. *Psychological Medicine*, 24, 145–153.

Kelly, K. G., Zisselman, M., Cutillo-Schmitter, T., Reichard, R., Payne, D. and Denman, S. J. (2001). Severity and course of delirium in medically hospitalized nursing facility residents. *American Journal of Geriatric Psychiatry*, 9, 72–77.

Kiely, D. K., Bergmann, M. A., Jones, R., Murphy, K. M., Orav, E. J. and Marcantonio, E. (2004). Characteristics associated with delirium persistance among newly admitted post-acute facility patients. *Journal of Gerontology: Medical Sciences*, 59A, 344–349.

Kiely, D. K., Jones, R., Bergmann, M. A., Murphy, K. M., Orav, E. J. and Marcantonio, E. (2006). Association between delirium resolution and functional recovery among newly admitted post-acute facility patients. *Journal of Gerontology: Medical Sciences*, 61A, 204–208.

Kiely, D. K., Jones, R., Bergmann, M. A. and Marcantonio, E. (2007). Association between psychomotor activity delirium subtypes and mortality among newly admitted post-acute facility patients. *Journal of Gerontology: Medical Sciences*, 62A, 174–179.

Kiely, D. K., *et al.* (2009). Persistent delirium predicts greater mortality. *Journal of the American Geriatrics Society*, 57, 55–61.

Knaus, W., Draper, E., Wagner, D. and Zimmerman, J. E. (1985) APACHE II: a severity of disease classification system. *Critical Care Medicine*, 13, 818–829.

Koponen, H., Stenbäck, U., Mattila, E., Soininen, H., Reinikainen, K. and Riekkinen, P. J. (1989). Delirium among elderly persons admitted to a psychiatric hospital: clinical course during the acute stage and one-year follow-up. *Acta Psychiatrica Scandinavica*, 79, 579–585.

Lawlor, P. G. *et al.* (2000). Occurence, causes, and outcome of delirium in patients with advanced cancer: a prospective study. *Archives of Internal Medicine*, 160, 786–794.

Lawton, M. P., Casten, R., Parmelee, P. A., van Haitsma, K., Corn, J. and Kleban, M. H. (1998). Psychometric characteristics of the minimum data set II: validity. *Journal of the American Geriatrics Society*, 46, 736–744.

Leonard, M. *et al.* (2008). Reversibility of delirium in terminally ill patients and predictors of mortality. *Palliative Medicine*, 22, 848–854.

Levkoff, S. E. *et al.* (1992). Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. *Archives of Internal Medicine*, 152, 334–340.

Levkoff, S. E. *et al.* (1994). Progression and resolution of delirium in elderly patients hospitalized for acute care. *American Journal of Geriatric Psychiatry*, 2, 230–238.

Lipowski, Z. J. (1987). Delirium (acute confusional states). *JAMA*, 258, 1789–1792.

Mahoney, F. I. and Barthel, D. W. (1965). Functional evaluation: the Barthel Index. *Maryland State Medical Journal*, 14, 61– 65.

Manos, P. J. and Wu, R. (1997). The duration of delirium in medical and postoperative patients referred for psychiatric consultation. *Annals of Clinical Psychiatry*, 9, 219–226.

Marcantonio, E., Flacker, J. M., Michaels, M. and Resnick, N. M. (2000). Delirium is independently associated with poor functional recovery after hip fracture. *Journal of the American Geriatrics Society*, 48, 618–624.

Marcantonio, E. R. *et al.* (2005) Outcomes of older people admitted to post acute facilities with delirium. *Journal of the American Geriatrics Society*, 53, 963–969

McAvay, G. J. *et al.* (2006). Older adults discharged from the hospital with delirium: 1-year outcomes. *Journal of the American Geriatrics Society*, 54, 1245–1250.

https://doi.org/10.1017/S1041610209991517 Published online by Cambridge University Press

McCusker, J., Cole, M., Bellavance, F. and Primeau, F. (1998). Delirium: reliability and validity of a new measure of severity of delirium. *International Psychogeriatrics*, 10, 421–433.

McCusker, J., Cole, M., Abrahamowicz, M., Primeau, F. and Belzile, E. (2002). Delirium predicts 12-month mortality. *Archives of Internal Medicine*, 162, 457–463.

McCusker, J., Cole, M., Dendukuri, N., Han, L. and Belzile, E. (2003). The course of delirium in older medical inpatients. A prospective study. *Journal of General Internal Medicine*, 18, 696–704.

Morita, T., Tsunoda, J., Inoue, S. and Chihara, S. (2001). Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients. *Journal of Pain and Symptom Management*, 22, 997–1006.

Olofsson, S. M., Weitzner, M. A., Valentine, A. D., Baile, W. F. and Meyers, C. A. (1996). A retrospective study of the psychiatric management and outcome of delirium in the cancer patient. *Support Care Cancer*, 4, 351–357.

Pitkälä, K. H., Laurila, J. V., Strandberg, T. E. and Tilvis, R. S. (2005). Prognostic significance of delirium in frail oder people. *Dementia and Geriatric Cognitive Disorders*, 19, 158–163.

Rockwood, K. (1989). Acute confusion in elderly medical patients. *Journal of the American Geriatrics Society*, 37, 150–154.

Rockwood, K., Cosway, S., Carver, D., Jarrett, P., Stadnyk, K. and Fisk, J. (1999). The risk of dementia and death after delirium. *Age and Ageing*, 28, 551–556.

Rudberg, M. A., Pompei, P., Foreman, M. D., Ross, R. E, and Cassel, C. K. (1997). The natural history of delirium in older hospitalized patients: a syndrome of heterogeneity. *Age and Ageing*, 26, 169–174.

Sagawa, R., Akechi, T., Okuyama, T., Uchida, M. and Furukawa, T. A. (2009). Etiologies of delirium and their relationship to reversibility and motor subtype in cancer patients. *Japanese Journal of Clinical Oncology*, 39, 175–182.

Siddiqi, N., House, A. O. and Holmes, J. D. (2006). Occurrence and outcome of delirium in medical patients: a systematic literature review. *Age and Ageing*, 35, 350–364.

Speciale, S., Bellelli, G., Lucchi, E. and Trabucchi, M. (2007). Delirium and functional recovery in elderly patients (Letter to the Editor). *Journal of Gerontology: Medical Sciences*, 62A, 107–108.

Streiner, D. L. (1995). Research methods in psychiatry. Learning how to differ: agreement and reliability statistics in psychiatry. *Canadian Journal of Psychiatry*, 40, 60–66.

Trzepacz, P. T., Baker, R. W. and Greenhouse, J. (1988). A symptom rating scale for delirium. *Psychiatry Research*, 23, 89–97.

Tuma, R. and DeAngelis, L. M. (2000). Altered mental status in patients with cancer. *Archives of Neurology*, 57, 1727–1731.

https://doi.org/10.1017/S1041610209991517 Published online by Cambridge University Press