The association between cognitive impairment and functional outcome in hospitalised older patients: a systematic review and meta-analysis

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Abstract

Background: in hospitalised older adults, cognitive impairments are common and may be associated with functional outcomes. Our aim was to systematically review this association.

Method: we systematically searched MEDLINE, CINAHL, AMED and PsycINFO from inception to April 2016. Non-English language studies were filtered out at search stage. All types of studies were considered for inclusion except reviews, conference abstracts, dissertations, and case studies. *Population:* community-dwelling or institutionalised older adults aged 65 years or more, who are acutely hospitalised and have information on history of dementia and/or cognitive scores on admission. *Setting:* acute hospital (excluding critical care and subacute or intermediate care). *Outcome of interest:* change in a measure of physical function or disability between pre-admission or admission, and discharge or post discharge. This review was registered on PROSPERO (CRD42016035978).

Results: the search returned 5,988 unique articles, of which 34 met inclusion criteria. All studies were observational, with 30 prospective and 4 retrospective from 14 countries, recruiting from general medicine (n=11), geriatric medicine (n=11) and mixed (n=12) wards. Twenty-six studies (54,637 participants) were suitable for the quantitative synthesis. The meta-analysis suggested that cognitive impairment was associated with functional decline in hospitalised older adults (RR: 1.64; 95% CI: 1.45-1.86; $p<0.01$). Results were similar in subanalyses focusing on diagnosis of dementia (RR: 1.36; 95% CI: 1.05-1.76; $p=0.02$; n=2,248) or delirium (RR: 1.55; 95% CI: 1.31-1.83; $p<0.01$; n=1,677).

Conclusion: cognitive impairments seem associated with functional decline in hospitalised older people. Causality cannot be inferred, and limitations include low quality of studies and possible confounding.

Keywords

Cognitive Impairments

Functional Decline

Hospital

Frail Older Adults

Systematic Review

Background

In the UK people over the age of 65 account for almost two thirds of acute hospital beds [1]. With an ever increasing population of older people, that proportion is expected to grow, and with it the prevalence of cognitive impairments associated with ageing [2]. The prevalence of dementia in acute hospitals has been estimated to be between 13-63% [3,4], and the prevalence of delirium between 20-27% [5,6]. Delirium is commonly superimposed on dementia in older inpatients [4].

Following a stressor such as an illness or fall precipitating a hospital admission, many older people experience loss of physical function, and this may be one of the reasons for an increased length of hospital stay [7]. Cognitive impairments in older people have been associated with adverse outcomes following hospitalisation including increased mortality, impaired functional recovery, acquisition of new geriatric syndromes, and institutionalisation [8-11]. Cognitive impairment may make older hospitalised people more vulnerable to loss of function or may impact on their ability to regain function once lost, meaning that by discharge they may not be at their pre-admission level of function [12].

A prominent hypothesis in cognitive ageing is the existence of a 'common factor' responsible for age-related deterioration in cognitive and non-cognitive (e.g. motor) processes [13], and in healthy older adults, there is evidence of a positive association between performance on mobility measures and cognitive assessments [14]. Despite cognitive impairments being common in hospitalised older adults, their association with the risk of functional decline had been less studied. Our aim was to conduct a systematic review of the association between cognitive impairment and functional outcome in acutely hospitalised older people. We

focused on non-specific cognitive impairment, dementia or delirium, and their association with functional outcome.

Methods

Search strategy

A protocol of this review was registered on PROSPERO in 2016: CRD42016035978 [15]. The following databases were searched electronically: MEDLINE, CINAHL, AMED and PsycINFO. Non-English language studies were filtered out at search stage. All types of studies were considered for inclusion except reviews, conference abstracts, dissertations, and case studies. The search was performed from inception to April 2016 to identify any new studies.

Key terms and MeSH headings used to search electronic databases were synonyms of: "elderly" and "function" and "hospital" and "impaired cognition". The search strategy for the MEDLINE electronic database is in Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/.

The reference lists of included studies, identified reviews and our own personal literature databases were searched to identify any potential studies additional to those identified through the electronic searching. This did not include a forward citation search on included studies. In addition, we searched electronic databases using the names of authors of identified conference abstracts and dissertations to check for any related published articles.

Selection criteria

Population: community-dwelling or institutionalised older adults aged 65 years or more, who are acutely hospitalised and have cognitive information on admission. Definitions of cognitive impairment included a known diagnosis of dementia (e.g. present in the patients' medical records), and/or low scores on validated cognitive tests or delirium screening tools.

Studies that focused on specific populations of people who had suffered an acute stroke, an acquired brain injury or a fractured neck of femur as reason for admission were excluded. This was because previous systematic reviews suggested poor association between cognitive impairment and functional recovery in those patient groups [16,17]. If the study included a mixed population and the results could not be differentiated, the authors were contacted for further data; if no response was received, or if they were unable to provide the data the study was excluded.

Setting: acute hospital ward (i.e. excluding sub-acute or intermediate care such as inpatient rehabilitation). Acute hospital wards include surgical wards, but not critical care settings.

Outcomes of interest: any measure of physical function or disability at pre-admission or admission, and discharge or post discharge. All studies reporting the number of patients with and without a cognitive impairment that changed in function either from pre-admission or admission to discharge or post-discharge were included. Decline in function was defined as a functional score at follow up worse than at baseline. For studies without a measure of pre-admission function we also accepted a definition of functional decline based on the numbers of patients with and without a cognitive impairment that failed to regain independence or whose discharge or post discharge level of function was worse than at admission.

Study selection: two reviewers worked independently using the pre-set inclusion criteria to identify relevant studies. The reviewers screened the articles' titles and abstracts and classified each as relevant, not relevant or unsure. All articles screened by both reviewers as being not relevant were excluded. The reviewers then independently reviewed all other

papers in full, but only using classifications of relevant or not relevant. Any discrepancy or uncertainty regarding the eligibility of a study was discussed between the two reviewers (who read the full paper together) or with a third author until consensus was reached. If variables of interest were measured but not reported, attempts were made to contact the authors before classifying a study as not relevant. Following this, all articles classified as not relevant were excluded from the review and the reasons were documented. The Newcastle-Ottawa Scale [18] was used for assessing the quality of included nonrandomised studies.

Statistical analyses

The meta-analyses were performed using Review Manager (RevMan5.3). The risk ratio (RR) and 95% confidence intervals (CI) were calculated. A fixed effect Mantel–Haenszel meta-analysis was undertaken when the inconsistency value (I^2) was 50% or less and Chi^2 had $p \geq 0.10$. A random-effect Mantel–Haenszel meta-analysis was undertaken when I^2 was >50% and Chi2 had $p < 0.10$.

In addition to the main meta-analysis, subgroup meta-subanalyses were planned for three different cognitive categories:

1. Diagnosis of dementia.
2. Diagnosis of delirium.
3. Studies reporting a non-specific cognitive impairment as measured by a validated cognitive scale (e.g. Folstein's Mini-Mental Status Exam: MMSE or Pfeiffer's Short Portable Mental Status Questionnaire: SPMSQ).

In order to explore if the functional outcome of cognitively impaired patients was different on discharge compared to post-discharge from hospital, we conducted a subanalysis of studies that reported functional outcome after at least one month post-discharge.

For each cognitive impairment category, the pooled effect estimate was calculated as a weighted average and 95% CI of the individual studies.

Declaration of Sources of Funding

Our study did not require funding.

Results

Our search returned 5,988 unique articles. In addition, we emailed 47 authors, of whom 27 did not reply, 12 replied with quantitative data and 8 with qualitative data. Thirty-four articles met inclusion criteria. All studies were observational, with 30 prospective and 4 retrospective from 14 countries, recruiting from general medicine (n=11), geriatric medicine (n=11), general and geriatric medicine (n=3), cardiology (n=2), medical and surgical (n=1) and other mixed (n=6) wards. Twenty-six studies (54,637 participants) were suitable for the quantitative synthesis, and 8 for the qualitative synthesis. Figure 1 shows the flow diagram of selected studies as per PRISMA guidelines [19]. As regards the type of cognitive impairment, 8 studies included information on dementia, 11 on delirium and 21 on non-specific cognitive impairment, but there was overlap within some studies (Table 1). As regards the timing of the functional measurements, 18 studies included information on admission and discharge, and 13 at pre-admission and post-discharge (at variable time points), with some overlap within studies as well (Table 1). Further details of the included studies, including the results of the risk of bias assessment, are summarised in Table 1. In addition, information regarding the inclusion and exclusion criteria of individual studies, definitions of functional decline and cognitive impairment, and other patient characteristics (e.g. mean age, length of hospital stay and proportion of patients with cognitive impairment) can be found in Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/. The overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines [20] was considered as 'low'.

Cognitive impairment versus no cognitive impairment (all studies)

Results are presented in Appendix 3a in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/. The meta-analysis of the 26 studies suggested that

cognitive impairment was associated with a statistically significant higher risk of hospitalisation-related functional decline: RR: 1.64; 95% CI: 1.45-1.86; $p<0.01$; n=54,637.

Appendix 3b in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/ shows a subanalysis of the 11 studies that included at least one month of follow up after discharge from hospital. Results were essentially unchanged (RR: 1.69; 95% CI: 1.44-1.98; $p<0.01$; n=37,808).

Dementia versus no dementia

Results are presented in Figure 2a. The meta-analysis of the six studies included suggested a statistically significant higher risk of functional decline during hospitalisation associated with a diagnosis of dementia: RR: 1.36; 95% CI: 1.05-1.76; $p=0.02$; n=2,248.

In a study included in the qualitative synthesis, the presence of dementia was an independent predictor of poorer functional status at two months after hospitalisation, together with factors such as worse baseline functional status and quality of life, depth of coma (if any), lower serum albumin, depression, incontinence, being bedridden, medical record documentation of need for nursing home, and older age [21]. In contrast, a second study found dementia not to be a significant predictor of functional decline, but this was in the context of a nursing intervention targeted at factors that influence acute confusion or delirium [22].

Delirium versus no delirium

Results are presented in Figure 2b. The meta-analysis of the ten studies included showed a statistically significant increased risk of adverse functional outcome associated with a diagnosis of delirium: RR: 1.55; 95% CI: 1.31-1.83); $p<0.01$; n=1,677.

A study in the qualitative synthesis also showed that delirious patients in hospital experienced functional decline, together with longer stays, more complications, higher mortality rate, and cognitive decline [23]. However, another study suggested that delirium in acutely admitted patients is associated with functional decline only in those in whom the delirium does not resolve (i.e. 37% of those with prevalent delirium in this series) [24]. Finally, another study found delirium not to be a significant predictor of functional improvement [22].

Non-specific cognitive impairment versus no cognitive impairment

Results are presented in Figure 2c. The meta-analysis of the fourteen studies included suggested that a non-specific cognitive impairment was associated with a statistically significant increased risk of adverse functional outcome: RR: 1.77; 95% CI: 1.46-2.14; $p<0.01$; n=51,070.

The results of the meta-analysis were echoed in the qualitative synthesis. A study showed that patients at greatest risk of adverse functional outcomes at follow-up were older, had preadmission instrumental activities of daily living (IADL) disabilities and lower mental status scores on admission, and had been re-hospitalised [25]. In another study, logistic regression analysis identified three patient characteristics that were independent predictors of functional decline: increasing age, lower admission MMSE scores, and lower preadmission IADL function [26]. In Sleiman *et al.* [27], results were suggestive of an association between higher MMSE score and functional recovery. Finally, one study found that a medium-high score of the Rankin Scale, a deficit in the items of the MMSE and a low Barthel Index (BI) score on admission were associated with an increased risk of loss of autonomy [28].

Discussion

Summary of key findings

Our results suggest that cognitive impairments in older patients admitted to the acute hospital may increase the risk of functional decline on discharge and after hospitalisation. Our findings contrast with previous reviews in patients with hip fractures [16] and patients after stroke [17], which suggested that there was little or no evidence that cognitive impairment is associated with functional recovery.

Our meta-analysis of observational studies cannot infer causality on the association between cognitive impairment and functional decline in hospitalised older patients. Mechanisms are likely to be multifactorial and may be explained in multiple non-competing ways. Firstly, the severity of the acute illness that cognitively impaired patients present with may cause functional loss via direct inflammatory damage to the musculoskeletal system [29,30], and it has also been suggested that central nervous system inflammation may induce muscle atrophy via activation of the hypothalamic-pituitary-adrenal axis [31]. Secondly, a pre-existing neurological impairment may reduce the ability to recover from an initial illness-related functional loss [32], and it has been suggested that the primary trigger of sarcopenia may be neurogenic in origin based on the intimate relationship between the nervous and muscular system [33]; thirdly, cognitive impairment may be a marker of underlying frailty and general vulnerability [7]; lastly, it is also possible that some of the functional decline may be related to the hospital structure, organisational factors, and the processes of care, including timely access to specialist care and therapies [34].

Limitations of included studies

The exclusion of non-English articles in the search strategy is a potential selection bias. In addition, some of the studies included were purely retrospective in their design, while others excluded patients with severe cognitive impairment or dementia. However, the large study by Kruse *et al.* [35] focused on the functional outcomes of nursing home residents undergoing acute hospitalisation; this study showed that for many long-stay nursing home residents, substantial and sustained functional worsening was associated with acute hospitalisation. Therefore, we are reasonably confident that our systematic review did not exclude the most vulnerable sector of older adults.

Another limitation was the considerable heterogeneity across studies in the methods used to assess function and diagnose cognitive impairment (for the details of individual studies, please see Appendix 2 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). For example, some studies [36-38] rely on a diagnosis of dementia based on the past medical history recorded in the case notes. There is evidence that only 35-50% of patients with dementia have a diagnosis on admission to hospital [4,39], and key assessments with regard to cognitive functioning are often missing in hospitals [40]. As regards delirium, most studies did not differentiate between those who recovered and those who did not, in terms of their functional outcomes. However, a previous study showed that the risk of poor functional recovery can be as high as 70% in complex delirious patients in hospital [9,41]. Not uncommonly, delirium is neither benign nor reversible, with a significant proportion of patients not experiencing restoration *ad integrum* of cognition and function [42]. The subanalysis of cognitive impairment categories (e.g. dementia versus delirium) is unlikely to be a ‘clean’ one, because delirium is commonly superimposed on dementia in older inpatients [4], and this natural overlap may also be present in research studies.

A further limitation is that we investigated cognition as a dichotomous variable, so we cannot make any assumptions about the impact of severity of cognitive impairment on the risk of functional decline. The same applies to the functional outcome definition. In addition, likely confounders such as comorbidity, frailty, acute illness severity, availability of therapy and social care factors may also be substantial contributors to functional decline, and the meta-analysis could not control for these issues. A notable exception was the large study in nursing home residents by Kruse *et al*. [35], the data of which was extracted from an 'ADL slope' model that calculated a predicted value for patients, after adjusting by age, gender, Charlson comorbidity index, baseline cognition, baseline ADL, primary diagnosis and length of hospital stay. Otherwise, the data included in the meta-analysis was unadjusted.

In addition, we looked at cognition at a single time point (i.e. admission), in association with physical function change (i.e. at two time points) without necessarily taking account of prior (i.e. premorbid) ability. The heterogeneity in the observation time points for the collection of functional information is also a limitation, but the subanalysis of studies that included at least one month of follow up after discharge did not significantly change the results (see Appendix 3b in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). Finally, exclusion of studies in intermediate care environments could mean that those that may have improved functionally by discharge (from therapy interventions) were excluded from the review.

Limitations of the review

A major limitation of this meta-analysis is the potential confounding introduced through low quality observational studies. Causality cannot be inferred. In addition, the review is limited by the fact that we only included studies published in English language.

Prospective research is needed to clarify the causal role and relative contributions of biological, physiological and extrinsic factors towards hospital-associated loss of function in older adults; however, important questions also need to be answered as regards the role of in-hospital Comprehensive Geriatric Assessment (CGA) and interventions. There is evidence that frail patients undergoing CGA in the hospital are more likely to be alive and at home after hospital discharge [43]; and it has been suggested that gerontologically attuned hospital environments can minimise incident disability and maximise recovery of compromised activities along and after the acute event [28]. For example, in one study, a nursing intervention employed strategies to educate staff, mobilise patients, monitor medication and make environmental and sensory modifications; and subjects who received the intervention were more likely to improve in functional status from admission to discharge than subjects who did not receive the intervention [22].

Conclusion

This systematic review suggested that cognitive impairment is associated with functional decline in acutely hospitalised older people. However, the association seen in observational studies does not imply causation. While some of the factors driving this association may be biological and related to acute illness severity and impaired ability to recover from stressors, some may be amenable to intervention, including physical interventions [44]. A limitation is that the overall quality of evidence according to the GRADE guidelines was low. Research is needed to elucidate causal mechanisms, including the relative contributions of intrinsic versus

extrinsic factors. For example, future prospective interventional studies of extra physical and/or cognitive stimulation in hospitalised patients with cognitive impairment may be able to elucidate if the functional decline can be minimised by interventions after accounting for confounders such as comorbidity, frailty, acute illness severity and social care factors.

Key points

- We reviewed the association between cognitive impairment and functional outcome in hospitalised older adults.
- Twenty-six studies (54,637 participants) were suitable for the quantitative synthesis.
- Cognitive impairment was associated with a higher risk of functional decline (RR: 1.64; 95% CI: 1.45-1.86; $p<0.01$).
- Research is needed to elucidate the causal mechanisms independently of confounders.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

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Conflicts of interest

None declared.

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PLEASE NOTE: the very long list of references supporting this review has meant that only the first 30 are listed here. The full list of references is available on the journal website http://www.ageing.oxfordjournals.org/ as Appendix 4.

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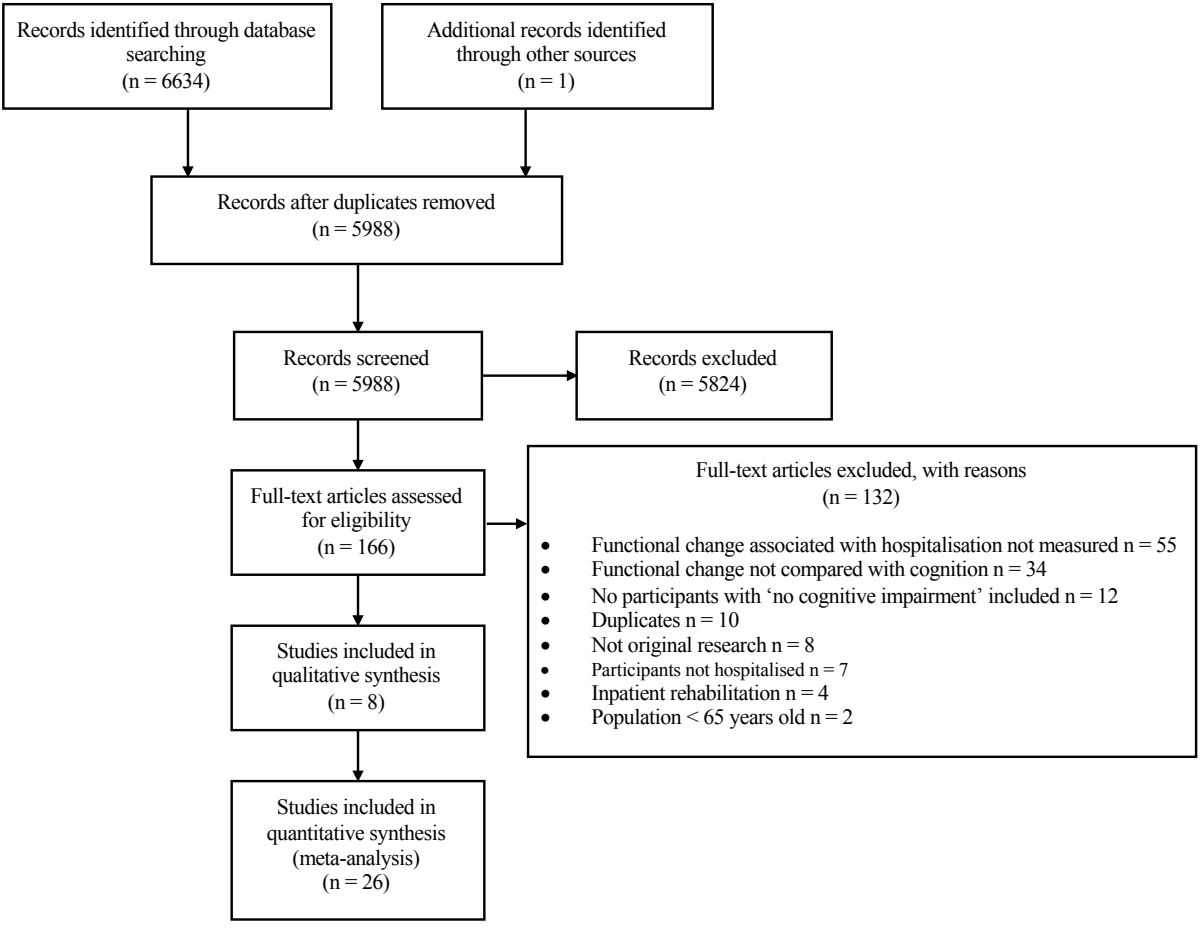

Records identified through database searching (n = 6634)
Additional records identified through other sources (n = 1)
Records after duplicates removed (n = 5988)
Records screened (n = 5988)
Records excluded (n = 5824)
Full-text articles assessed for eligibility (n = 166)
Full-text articles excluded, with reasons (n = 132)
Functional change associated with hospitalisation not measured n = 55
Functional change not compared with cognition n = 34
No participants with 'no cognitive impairment' included n = 12
Duplicates n = 10
Not original research n = 8
Participants not hospitalised n = 7
Inpatient rehabilitation n = 4
Population < 65 years old n = 2
Studies included in qualitative synthesis (n = 8)
Studies included in quantitative synthesis (meta-analysis) (n = 26)

Figure 2a

Study or Subgroup	Dementia Events	Dementia Total	No Dementia Events	No Dementia Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnes 2012	23	60	97	389	19.3%	1.54 [1.07, 2.21]
Hartley 2016	29	138	102	452	19.2%	0.93 [0.65, 1.34]
McCusker 2001	32	184	16	82	13.2%	0.89 [0.52, 1.53]
Mudge 2010	41	50	184	337	27.8%	1.50 [1.28, 1.77]
Naruishi 2014	13	150	7	112	6.7%	1.39 [0.57, 3.36]
Zekry 2011	40	148	17	146	13.8%	2.32 [1.38, 3.90]
Total (95% CI)		**730**		**1518**	**100.0%**	**1.36 [1.05, 1.76]**
Total events	178		423			

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 12.67$, df = 5 (P = 0.03); $I^2 = 61\%$
Test for overall effect: Z = 2.31 (P = 0.02)

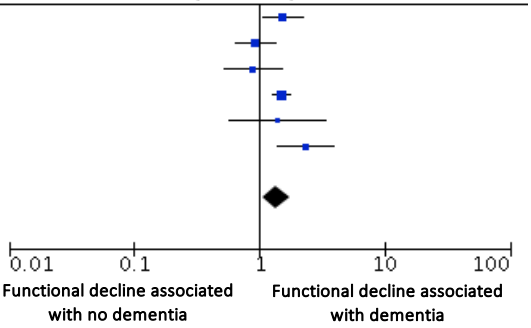


Figure 2b

Study or Subgroup	Delirium Events	Delirium Total	No delirium Events	No delirium Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2010	6	10	57	107	7.2%	1.13 [0.66, 1.93]
Francis 1992	8	20	21	115	4.6%	2.19 [1.13, 4.24]
Friedman 2008	15	35	30	113	10.6%	1.61 [0.99, 2.64]
Hansen 1999	3	5	40	68	4.1%	1.02 [0.49, 2.14]
Inouye 1993	18	43	33	145	11.2%	1.84 [1.16, 2.92]
McCusker 2001	32	179	16	87	16.0%	0.97 [0.56, 1.67]
Murray 1993	38	91	51	200	23.7%	1.64 [1.17, 2.30]
Noriega 2015	10	35	21	168	5.4%	2.29 [1.18, 4.42]
O'Keeffe 1997	12	47	15	124	6.1%	2.11 [1.07, 4.17]
Velilla 2012	40	63	10	22	11.0%	1.40 [0.85, 2.29]
Total (95% CI)		**528**		**1149**	**100.0%**	**1.55 [1.31, 1.83]**
Total events	182		294			

Heterogeneity: $Chi^2 = 9.42$, df = 9 (P = 0.40); $I^2 = 4\%$
Test for overall effect: Z = 5.20 (P < 0.00001)

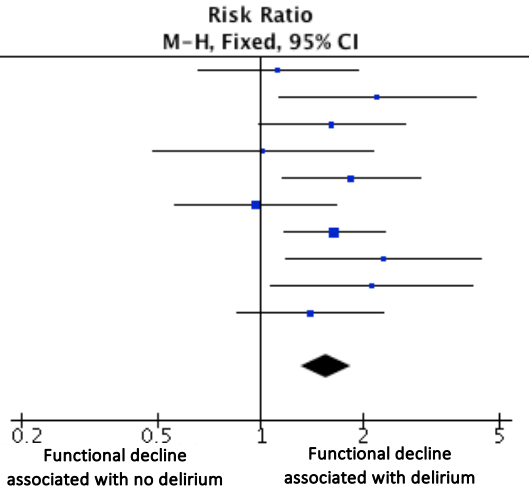
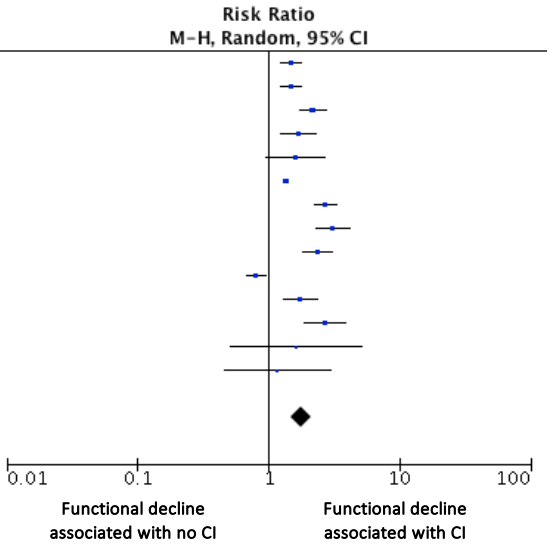


Figure 2c

Study or Subgroup	CI Events	CI Total	No CI Events	No CI Total	Weight	Risk Ratio M-H, Random, 95% CI
Bo 2016	189	619	151	736	8.6%	1.49 [1.24, 1.79]
Chaudhry 2004	220	459	131	403	8.7%	1.47 [1.24, 1.75]
Cornette 2005	59	107	106	415	8.1%	2.16 [1.70, 2.74]
Hansen 1999	13	15	30	58	7.4%	1.68 [1.22, 2.30]
Inouye 1993	12	31	38	157	5.5%	1.60 [0.95, 2.70]
Kruse 2013 (1)	9311	20785	4281	13035	9.3%	1.36 [1.33, 1.40]
Mehta 2011	90	151	162	734	8.5%	2.70 [2.24, 3.26]
Pedone 2005	76	1903	93	7158	7.6%	3.07 [2.28, 4.14]
Sands 2003	73	217	113	796	8.0%	2.37 [1.84, 3.05]
Socorro 2015	136	442	223	581	8.6%	0.80 [0.67, 0.95]
Sánchez 2011	27	39	49	123	7.6%	1.74 [1.29, 2.35]
Volpato 2007	47	355	66	1331	7.1%	2.67 [1.87, 3.81]
von Renteln-Kruse 2015	24	197	3	40	2.1%	1.62 [0.51, 5.14]
Zekry 2011	5	37	17	146	2.9%	1.16 [0.46, 2.94]
Total (95% CI)		**25357**		**25713**	**100.0%**	**1.77 [1.46, 2.14]**
Total events	10282		5463			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 162.42$, df = 13 (P < 0.00001); $I^2 = 92\%$
Test for overall effect: Z = 5.79 (P < 0.00001)



Footnotes
(1) Random slopes as predicted by the model as oppose to actual data points

Appendix 1. Medline search strategy.

1. (Dement* or deliri* or confus* or cogniti* or Alzheimer* or "mental status")
2. (MH "Memory Disorders+")
3. (MH "Delirium, Dementia, Amnestic, Cognitive Disorders+")
4. #1 or #2 or #3
5. "older person*" or "older adult*" or "older people*" or Frail* or elderly or geriatric*
6. (MH "Frail Elderly") OR (MH "Aged+")
7. #5 or #6
8. AB (MRMI "rivermead index" or EMS or "elderly mobility scale" or BI or "Barthel Index" or mRS or Rankin or FIM or "functional independence measure" or FAC "functional ambulatory category" or IADL or ADL or "activit* of daily living" or Katz)) OR TI (function* or mobil* or or dependen* or independen* or Disab* or ADL or IADL or activit*))))
9. (MH "Rehabilitation+") or (MH "Recovery of Function") or (MH "Mobility Limitation") or (MH "Independent Living") or (MH "Activities of Daily Living")
10. #8 or #9
11. TI (hospital* or inpatient* or in-patient* or acute or subacute or sub-acute or "secondary care")
12. (MH "Secondary Care") or (MH "Hospitalization+") or (MH "Inpatients")
13. #11 or #12
14. #4 and #7 and #10 and #13
15. Limit to English language

Appendix 2. Further data of included studies.

Author and year	Study design	Setting	Inclusion criteria	Exclusion criteria	Sampling	Definition of deterioration in function	Definition of cognitive impairment	Patient characteristics
Adamis *et al.* 2011 [24]	Prospective Cohort Study	Elderly Medical Unit	Age 70 or older; admitted to the elderly medical Unit within 3 days of admission	Thought to be terminally ill; included in the study on an earlier admission	Not specified	Deterioration definition not specifically defined, study reported on change in BI from admission to discharge	Delirium diagnosed per CAM criteria NSCI diagnosed with MMSE, cut-off not specified	Mean age: 84.6 Percentage with cognitive impairment: 26% Mean length of hospital stay: 19 days
Barnes *et al.* 2013 [36]	Retrospective Cohort Study	General Medical Service of University Hospitals	Age 70 or older; admitted to general medical service of 1 of 2 hospitals; fully independent in ADLs 2 weeks before admission and dependent in 1 or more ADLs at discharge	Elective admissions; admissions to Intensive Care Unit or subspecialty units; and those with a length of stay less than 2 days	A subset from 2 randomised control trials	Patients categorised into those who had recovered independence in ADLs, or remained dependent in 1 or more ADLs in the year following hospitalisation	NSCI defined as more than 5 errors on the SPMSQ	Mean age: not reported (age 70–79: n=198, age 80–89: n=191, age ≥90: n=60) Percentage with cognitive impairment: 13% Average length of hospital stay: not reported
Bo *et al.* 2016 [45]	Prospective Cohort Study	8 acute Geriatric and Medical Wards of 2 University Hospitals	Age 65 years or older; admitted from the Emergency Department	Patients from Intensive Care Units, other hospitals, or other departments, and those who died or were discharged within 24 hours of admission	Consecutive admissions	A lower ADL score (1 or more) (increase in dependence) at discharge compared to admission, excluding those completely dependent on admission	Mild NSCI defined as 3-4 errors on the SPMSQ Moderate to severe NSCI defined as more than 5 errors on the	Mean age: 81.3 Percentage with cognitive impairment: 46% Median length of hospital stay: 11 days

							SPMSQ	
Chaudhry *et al.* 2004 [46]	Prospective Cohort Study	General Medical Service of Teaching Hospital	Age 70 or older; willing and able to participate in interviews; had 1 of the following risk factors for delirium: visual impairment, severe illness, cognitive impairment, high blood urea nitrogen to creatinine ratio	Length of stay less than 48 hours, terminal illness, died during hospital admission or missing data on level of education or functional status at 6 months	Consecutive admissions	A lower ADL score (1 or more) (increase in dependence) at follow up than at pre-admission baseline	MMSE categorised into: 5-9, 10-15, 15-19, 20-24, more than or equal to 25. For meta-analysis NSCI defined as MMSE less than 25	Mean age: not reported (age: 70-79 n=37, age: 80-89 n=43, age: 90-99 n=52) Percentage with cognitive impairment: 53% Average length of hospital stay: not reported
Chen *et al.* 2010 [47]	Prospective Cohort Study	Geriatric Unit of a General Hospital	Age over 65; admitted to Geriatric Unit due to geriatric syndromes, or development of ADL dependence within 2 weeks before admission because of acute illness, as well as those referred from other wards for rehabilitation after stabilisation of an acute illness	Completely physically dependent before admission; had cancer with metastasis, had a known severe dementia before admission; with expected survival of less than 6 months; experiencing rapid recovery of physical dependence	Not specified	Functional recovery determined by improvement in the BI after discharge intervention of more than 10%	NSCI defined as MMSE less than 24 for literate and less than 14 for illiterate patients	Mean age: 80 Percentage with cognitive impairment: 9% Mean length of hospital stay: 16 days
Cornette *et al.* 2006 [48]	Prospective Cohort Study	2 General Academic Hospitals	Age 70 or older; admitted via the Emergency Department	Length of stay less than 48 hours; terminal illness; admission to the Intensive Care Unit; admission for a stroke; dependence in all ADLs	Not specified	Loss of at least 1 point on the ADL scale (increase in dependence) between premorbid evaluation on admission and 3-month post-discharge evaluation	NSCI defined as shortened version of MMSE less than15 (max score of 21)	Mean age: 80 Percentage with cognitive impairment: 21% Average length of hospital stay:

								not reported
Feldman *et al.* 1999 [23]	Prospective Cohort Study	Acute Geriatric Unit of a University Hospital	Age 70 or older; first admission to Geriatric Unit during study period	Not admitted to the Geriatric Unit on the day of admission to the hospital; admitted electively for investigations or rehabilitation; aphasia or deafness; expected to remain in the hospital for less than 48 hours; moribund conditions; not assessed by a study doctor within 48 hours of admission	Consecutive admissions	Increase in ADL score (increase in dependence) between admission and discharge	Delirium diagnosed per CAM and DRS criteria	Mean age: 81 Percentage with cognitive impairment: 18% Mean length of hospital stay: 9
Francis *et al.* 1992 [49]	Prospective Cohort Study	General Medical Service from University Hospital	Age 70 or older; living in the community and admitted to General Medical Service	Transferred from other hospitals, or Nursing Homes; terminal illness; severe dementia requiring continual assistance in ADLs; admitted for less than 48 hours; aphasia, deafness, blindness; inability to speak English	Consecutive admissions	Institutionalised or needing assistance with ADLs at follow-up (2 years), having been independent with all ADLs at pre-admission baseline	Delirium diagnosed per DSM-III-R criteria	Mean age: 78 Percentage with cognitive impairment: 22% Mean length of hospital stay: not stated
Friedman *et al.* 2008 [50]	Prospective Cohort Study	Acute Elderly Care Unit in a Community Hospital	Admitted to Elderly Care Unit	n/a	Consecutive admissions	Increase in ADL score (increase in dependence) between admission and discharge (excluding those with full dependency on admission)	Delirium diagnosed per CAM criteria	Mean age: 79 Percentage with cognitive impairment: 19% Mean length of hospital stay: 5

Hansen *et al.* 1999 [51]	Prospective Cohort Study	Hospital	Age 65 or older, admitted for a medical (non-surgical, non-psychiatric illness)	Enrolment in hospice; diagnosis of metastatic cancer; new CVA or MI within the last 2 months; diagnosis of dementia if no caregiver in the home; more than 4 days between hospital discharge and home health enrolment; non-ambulatory status; miscellaneous, including "inability to speak English, anticipated move from the community in the next week, etc."	Not specified	Sub-group analysis of patients who were completely independent in ADLs at pre-admission baseline but dependent in 1 or more ADL by discharge. Patients were categorised as having regained independence or remaining dependent at 1 month after discharge.	Delirium diagnosed per CAM criteria NSCI defined as MMSE score of less than 24	Mean age: 80 Percentage with cognitive impairment: 21% Mean length of hospital stay: 8 days
Hartley *et al.* 2016 [37]	Retrospective Cohort Study	Geriatric Wards of University Hospital	First admission episodes to the Geriatric Wards from within county borders	Patients who died during admission	Consecutive admissions	Increase in modified Rankin Scale (increase in dependence) of at least 1 point from pre-admission baseline to discharge (excluding those with full dependence on admission)	Dementia based on medical chart review	Mean age: 86 Percentage with cognitive impairment: 45% Mean length of hospital stay: 15 days
Inouye *et al.* 1993 [52]	2 Prospective Cohort Studies (development cohort and validation cohort) running in tandem	General Medical Wards of a University Hospital	Age 70 or older, admitted to General Medical Wards	Unable to be interviewed (e.g. intubation, coma, severe aphasia); terminal condition; discharged within 48 hours; completely dependent in all ADLs at baseline; had been enrolled in the study on a previous	Pragmatic convenience sampling (i.e. 234 patients not evaluated for logistical reasons such as weekend enrolments and unavailability of research staff)	A change from being independent to requiring partial or total assistance with an ADL, or a change from requiring partial assistance to total assistance by discharge	NSCI defined as MMSE score less than 20 Delirium diagnosed per CAM criteria	Mean age: 78 Percentage with cognitive impairment: 30% Median length of hospital stay: 7 days

				admission				
Kruse *et al.* 2013 [35]	Longitudinal Cohort Study	Hospitals and Nursing Homes	Age 67 or older; Nursing Home resident with an episode of acute hospitalisation of 30 or fewer days, and having at least 2 preceding assessments with ADL data, 1 of which was within the 30 days preceding hospitalization	Various reasons based on lacking data; residents with date discrepancies (e.g., multiple dates of death); and residents with more than 15 acute hospitalisations in 2006 and 2007; residents who died in hospital; residents who did not reside in 1 facility for all included assessments	All patients within a national database	Worsening ADL function defined as gain of 3 or more points (increase in dependence) in the 6 months post discharge	NSCI defined as a CPS score of 3-6	Mean age: not stated (52% were age 85 years or older) Percentage with cognitive impairment: 62% Mean length of hospital stay: not stated
McCusker *et al.* 2001 [53]	Prospective Cohort Study	Medical Services of University Hospital	Age 65 or older, admitted from the Emergency Department.	A primary diagnosis of stroke; admitted to an Oncology Unit, Intensive Care Unit, Cardiac Monitoring Unit (unless they were transferred to a Medical Ward within 48 hours of admission); those who didn't speak English or French	Not specified	1 point loss in BI (increase in dependence) from admission to discharge	Delirium diagnosed per CAM criteria Dementia using the IQCODE with a cut-off of 3.5 for diagnosing dementia.	Mean age: not reported Percentage with cognitive impairment: 87% Mean length of hospital stay: not stated
Mehta *et al.* 2011 [54]	Secondary data analyses of 2 Prospective Studies	Medical Services of 2 Teaching Hospitals	70 or older who had emergency admissions to the General Medical Services; independent with ADLs 2 weeks before admission	Admission to an Intensive Care Unit or Oncology Ward; elective admission or length of stay less than 2 days	Consecutive sampling	New-onset disability, defined as a new need for personal assistance in 1 or more ADLs at discharge in participants who were independent 2 weeks before hospital admission	NSCI defined as more than 5 errors on the SPMSQ	Mean age: 78 Percentage with cognitive impairment: 17% Mean length of hospital stay: not stated
Mercante *et al.* 2014 [28]	Prospective Cohort Study	Hospital	Age 65 or older	Admitted for less than 24 hours; admitted to day hospital or to day surgery	Not specified	Decrease of at least 5 counts (increase in dependence) between modified	NSCI diagnosed using 4 items derived from	Mean age: 82 Percentage with

						BI at discharge compared to admission	MMSE	cognitive impairment: 12.7% Mean length of hospital stay: 10
Mudge *et al.* 2010 [55]	Secondary data analysis of a Prospective Control Study	Internal Medicine Service of a Teaching Hospital	Age over 65	Died in hospital; fully dependent in ADLs at pre-admission baseline; length of stay less than 2 days	Consecutive admissions	Increase in ADL score of 1 or more point (increase in dependence) between pre-admission baseline and admission which failed to return to (or lower than) pre-admission baseline level by discharge	Dementia based on medical chart review	Mean age: 80 Percentage with cognitive impairment: 10% Median length of hospital stay: 7 days
Murray *et al.* 1993 [38]	Prospective Cohort Study	Medical and Surgical Units of Teaching Hospital	Age over 65, from 2 populations: a geographically defined community or from a Nursing Home	Direct admissions from an Intensive Care Unit or Psychiatric Unit; severe language or hearing problems; actively contagious tuberculosis; lacked an available proxy; delirium upon admission evaluation	Consecutive admissions	Increase in ADL score of 1 point or more (increase in dependence) from pre-admission baseline to 3 months post discharge	Delirium diagnosed as per DSM-III criteria Dementia based on medical chart review	Mean age: 81 Percentage with cognitive impairment: 31 Average length of hospital stay: not stated
Naruishi *et al.* 2014 [56]	Retrospective Cohort Study	Hospital	Age over 70	Not specified	Not specified	Decrease in FIM of 1 or more points (increase in dependence) from admission to discharge	NSCI diagnosed as per CDR criteria	Mean age: 83 Percentage with cognitive impairment: 57% Mean length of hospital stay: 33
Noriega *et al.* 2015 [57]	Prospective Cohort Study	Cardiology Department of a University	Age 75 or older; direct urgent admission to the Cardiology	Scheduled hospitalisations; terminal status in the first 24 hours after	Consecutive admissions	Loss of at least 1 point in the ADL scale (increase in dependence) at	Delirium diagnosed per CAM criteria	Mean age: 82 Percentage with cognitive

		Hospital	Department	admission; delirium at admission making patients unable to participate in the study		discharge compared to pre-admission baseline		impairment: 17% Mean length of hospital stay: 7
O'Keeffe *et al.* 1997 [58]	Prospective Cohort Study	Acute Geriatric Unit of Hospital	First admission to acute Geriatric Unit during study period	Not admitted to the Geriatric Unit on the day of admission; admitted electively for investigations, rehabilitation, or respite care; severe aphasia or deafness; expected to remain in hospital less than 48 hours; not assessed by a study doctor within 48 hours of admission	Consecutive admissions	Loss of at least 1 point in the ADL scale (increase in dependence) at discharge compared to admission.	Delirium diagnosed per DAS and DSM-III criteria	Mean age: 82 Percentage with cognitive impairment: 42% Mean length of hospital stay: 15
Pedone *et al.* 2005 [59]	Prospective Cohort Study	Geriatric and Internal Medicine Wards of 83 centres	Age over 65	Death during hospitalisation; admission ADL score equal to 0 (full dependence); missing functional data; length of stay more than 90 days; "mental retardation"	Consecutive admissions	Loss of at least 1 point in the ADL scale (increase in dependence) at discharge compared to admission	NSCI defined as a score of less than 6 on the HAMT	Mean age: 77 Percentage with cognitive impairment: 21% Mean length of hospital stay: 15
Sager, Franke *et al.* 1996 [25]	Prospective Cohort Study	3 University Hospitals, 2 Private Acute Care Hospitals	Age 70 or older; hospitalised for acute medical illness	Terminal illness; severe cognitive impairment with inability to give informed consent; admission to an Intensive Care Unit; living in Nursing Home before admission; admitted for surgical diagnoses; died in hospital	Not specified other than a "subgroup of patients"	Loss of at least 1 point in the ADL scale (increase in dependence) at 3 months post discharge compared to pre-admission baseline	NSCI measured with shortened MMSE (range 0-21), cut off point not used	Mean age: 79 Percentage with cognitive impairment: not reported Mean length of hospital stay: 9 days
Sager,	2 Prospective	4 University	Age 70 or older;	Terminal illness;	Not specified	Loss of at least 1	NSCI	Mean age: 79

Rudberg *et al.* 1996 [26]	Cohort studies (development cohort and validation cohort)	hospitals and 2 Private Acute Care Hospitals	hospitalised for acute medical illness	severe cognitive impairment with inability to give informed consent; admission to an Intensive Care Unit; living in Nursing Home before admission; died in hospital or died 3 months post discharge	other than patients enrolled in 2 clinical trials of the "Hospital Outcomes Project for the Elderly"	point in the ADL scale (increase in dependence) at discharge and at 3 months post discharge compared to pre-admission baseline	measured with shortened MMSE (range 0-21), cut of point of less than 15	Percentage with cognitive impairment: not reported Mean length of hospital stay: 8 days
Sanchez *et al.* 2011 [60]	Prospective Cohort Study	Cardiology Department of University Hospital	Age 75 or older; admitted with acute cardiac condition; direct admission to cardiology department	Terminal status in the first 24 hours after admission; elective admission	Consecutive admissions	Loss of 1 point in the ADL scale (increase in dependence) at 12 months post discharge compared to pre-admission baseline	NSCI defined with Spanish version of MMSE (range 0-35), cut off point of less than 22	Mean age: 82 Percentage with cognitive impairment: 24% Mean length of hospital stay: 7 days
Sands *et al.* 2003 [61]	Secondary data analysis of 2 Control Studies	2 Teaching Hospitals	Age 70 or older; enrolled in 2 trials of an intervention to improve functional outcomes after hospitalisation	Patients with a length of stay shorter than 2 days; postoperative; admitted to subspecialty Medical Teams or Intensive Care Units	Taken from both control and intervention arm of 2 previous control trials	Loss of 1 point or more in the ADL scale (increase in dependence) from admission compared to discharge, in those that were completely independent in ADLs at pre-admission baseline	Mild NSCI: 3-4 errors on the SPMSQ Moderate to severe NSCI defined as more than 5 errors on the SPMSQ	Mean age: 80 Percentage with cognitive impairment: 42% Average length of hospital stay: not reported
Sleiman *et al.* 2009 [27]	Retrospective Cohort Study	Acute Geriatric Ward of Hospital	Patients admitted to an Acute Geriatric Ward	No change in function during hospitalisation; premorbid BI less than or equal to 10; diagnosed with a stroke; died in hospital	Consecutive sampling	Functional trajectory was assessed by evaluating functional decline at admission (difference between ADLs 15 days before and at admission) and	NSCI defined as MMSE of less than 18	Mean age: 81 Percentage with cognitive impairment: 27% Mean length of hospital stay: 7 days

						ability or inability to regain function (difference between ADLs at admission and at discharge)		
Socorro Garcia *et al.* 2015 [62]	Prospective Cohort Study	Acute Geriatric Unit of Hospital	Age 90 and over	Not specified	Not specified	Loss of 1 or more points in BI (increased dependence) at discharge compared to 2 weeks before admission	NSCI defined as CRM more than or equal to 2	Mean age: 94 Percentage with cognitive impairment: 50% Mean length of hospital stay: 11 days
Velilla *et al.* 2012 [63]	Prospective Cohort Study	Acute Geriatric Wards of 3 Hospitals	Age over 74; emergency admission to Acute Geriatric Wards	Impossibility to obtain informed consent within 2 working days; admission for palliative care; comatose; life expectancy less than 3 months; impossibility to get a family member or caregiver able to give truthful information and those suspected of alcohol withdrawal delirium	Consecutive sampling during a 48-hour observation period	Definition of decline in function not specified, but reported on change in BI at 30 days after discharge compared to admission	Delirium diagnosed as per CAM and DSM-III criteria	Mean age: 87 Percentage with cognitive impairment: 75% Mean length of hospital stay: not reported
Volpato *et al.* 2007 [64]	Longitudinal Observational Study	Geriatric and Internal Medicine Units of 81 centres	Age 65 or older; independent in ADLs 2 weeks before hospital admission	Missing functional data; died during hospital stay	Consecutive sampling	New ADL dependence by time of discharge from hospital	NSCI defined as AMT of more than 4 errors	Mean age: 77 Percentage with cognitive impairment: 21% Mean length of hospital stay: 11 days
von	Prospective	Department	Hospitalised and	Not specified	Consecutive	Loss of 1 or more	NSCI defined	Mean age: 82

Renteln-Kruse *et al.* 2015 [65]	Cohort Study	of Geriatric Medicine of Teaching Hospital	admitted to Geriatric Ward; first admission during study period		sampling	points in BI (increased dependence) at discharge compared to admission	as MMSE of less than 24	Percentage with cognitive impairment: 83% Mean length of hospital stay: 18 days
Wanich *et al.* 1992 [22]	Prospective Control study	Medical Units of Teaching Hospital	Age 70 or older; first admission during study period	Transferred from another Unit within the Hospital; admitted for a short stay procedure such as chemotherapy, transfusion, a diagnostic study or dialysis; admitted for terminal care; private physicians requested exclusion	Consecutive admissions between Sunday noon and Friday noon	Increase of 2 or more points in ADL score (increased dependence) from admission to discharge	Dementia method of diagnosis or identification not specified Delirium diagnosed as per DSM-III criteria	Mean age: 77 Percentage with cognitive impairment: 21% Mean length of hospital stay: 9 days
Wu *et al.* 2000 [21]	Prospective Cohort Study	4 Teaching Hospitals	Age 80 or older; an acute illness	Non-English language speakers; foreign national admitted specifically for a medical procedure; diagnosis of AIDS; sustained multiple trauma; admitted for hospice care; admitted to the psychiatric service; admitted for elective surgery; transferred from another hospital; died during the admission; discharged within 48 hours; scheduled to be discharged within 72 hours	"Hospitals with an abundance of available patients employed random enrolment at a suitable ratio in order to equalise enrolment at each of the study hospitals."	Poor functional status at 2 and 12 months (as measured by ADL scale) post discharge examined by logistic regression analysis after controlling for pre-admission baseline function (as measured by ADL scale)	Dementia method of diagnosis or identification not specified	Median age: 85 Percentage with cognitive impairment: 23% Average length of hospital stay: not reported
Zekry *et al.* 2011	Prospective Cohort Study	Geriatric Hospital	Age over 75	Disorders interfering with psychometric	Randomised sample of all	Decrease of 1 or more points	Mild NSCI diagnosed by	Mean age: 85

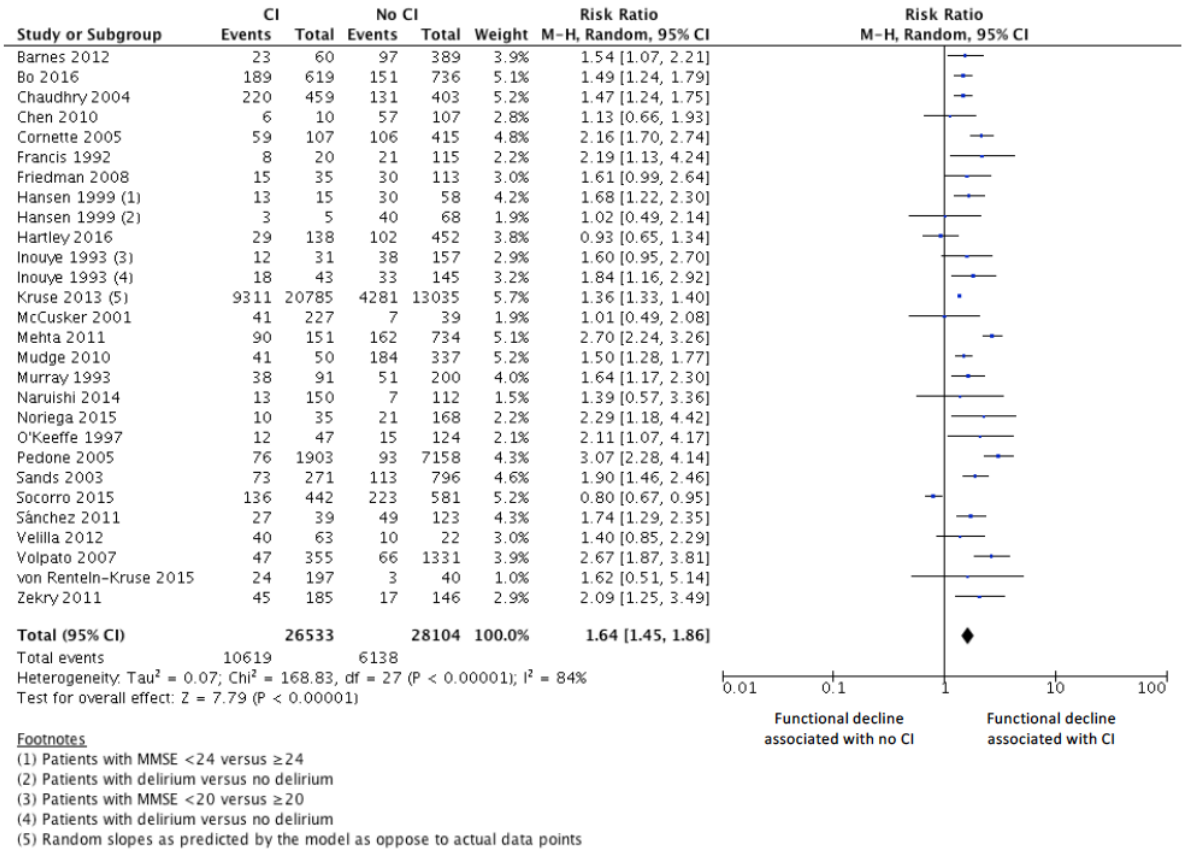
[66]				assessment (severe deafness or blindness, or major behavioural problems); terminal illness	admissions	(increase dependence) on FIM between admission and discharge	CDR score of 0.5, dementia diagnosed by CDR score of 1 or more	Percentage with cognitive impairment: 54% Mean length of hospital stay: 7 days

Abbreviations:
ADL: Activities of daily living
NSCI: Non-specific cognitive impairment

Abbreviations of Functional Assessment Tools:
ADL: Activities of Daily Living – (Various tools used, all similar to the Katz ADL scale)
BI: Barthel Index
mRS: modified Rankin Scale
FIM: Functional Independence Measure

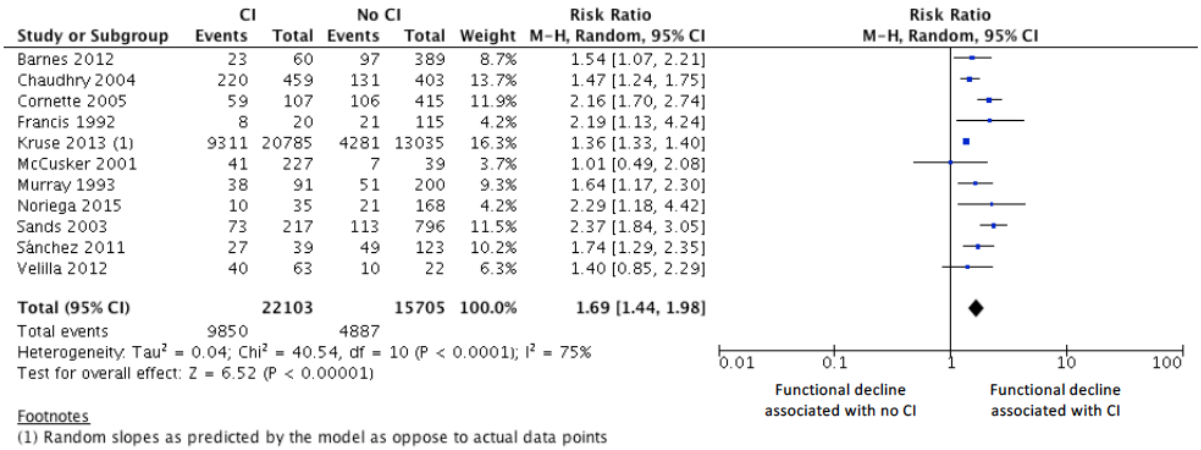
Abbreviations of Cognitive Screening Tools:
AMT: Abbreviated Mental Test
CAM: Confusion Assessment Method
CDR: Clinical Dementia Rating scale
CPS: Cognitive Performance Scale
CRM: Mental Scale of the Red Cross
DRS: Delirium Rating Scale
DSM-III/DSM-III-R/DSM-IV: Diagnostic and Statistical Manual of Mental Disorders
IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly
HAMT: Hodkinson Abbreviated Mental Test
MMSE: Mini mental state examination
SCEB: Short Cognitive Evaluation Battery
SPMSQ: Short portable Mental Status Questionnaire

Appendix 3a. Meta-analysis comparing the relative risk of functional decline between groups with and without cognitive impairment (all studies).



Footnotes
(1) Patients with MMSE <24 versus ≥24
(2) Patients with delirium versus no delirium
(3) Patients with MMSE <20 versus ≥20
(4) Patients with delirium versus no delirium
(5) Random slopes as predicted by the model as oppose to actual data points

Appendix 3b. Subanalysis of the studies that included at least 1 month follow up.



Study or Subgroup	CI Events	CI Total	No CI Events	No CI Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnes 2012	23	60	97	389	8.7%	1.54 [1.07, 2.21]
Chaudhry 2004	220	459	131	403	13.7%	1.47 [1.24, 1.75]
Cornette 2005	59	107	106	415	11.9%	2.16 [1.70, 2.74]
Francis 1992	8	20	21	115	4.2%	2.19 [1.13, 4.24]
Kruse 2013 (1)	9311	20785	4281	13035	16.3%	1.36 [1.33, 1.40]
McCusker 2001	41	227	7	39	3.7%	1.01 [0.49, 2.08]
Murray 1993	38	91	51	200	9.3%	1.64 [1.17, 2.30]
Noriega 2015	10	35	21	168	4.2%	2.29 [1.18, 4.42]
Sands 2003	73	217	113	796	11.5%	2.37 [1.84, 3.05]
Sánchez 2011	27	39	49	123	10.2%	1.74 [1.29, 2.35]
Velilla 2012	40	63	10	22	6.3%	1.40 [0.85, 2.29]
Total (95% CI)		**22103**		**15705**	**100.0%**	**1.69 [1.44, 1.98]**
Total events	9850		4887			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 40.54$, df = 10 ($P < 0.0001$); $I^2 = 75\%$

Test for overall effect: $Z = 6.52$ ($P < 0.00001$)

Footnotes

(1) Random slopes as predicted by the model as oppose to actual data points

Appendix 4. Full list of references.

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