Low peripheral levels of insulin growth factor-1 are associated with high incidence of delirium among elderly patients: A systematic review and meta-analysis

Running title: MA of IGF-1 and delirium

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Abstract:

Introduction: Delirium, a serious condition observed in critically ill patients, clinically presents with impaired cognition and consciousness. The relationship between delirium and peripheral levels of insulin growth factor-1 (IGF-1) is unclear. Thus we conducted a meta-analysis to address this issue.

Methods: Seven major electronic databases were searched from inception until October 2, 2017 to obtain relevant clinical variables to compare the difference in IGF-1 levels between delirious and non-delirious elderly in-patients. A random effects meta-analysis was conducted.

Results: We studies 10 articles involving 294 delirious patients (mean age 73.0 years) and 604 non-delirious patients (mean age 76.9 years). We found that peripheral levels of IGF-1 in patients with delirium were significantly lower than in those without delirium (Hedges` g = -0.209, 95% confidence interval [CI] = -0.393 to -0.026, p = 0.025). Meta-regression analyses found that no variables such as percentage of cognitive impairment, mean age, and female proportion contribute to heterogeneity in terms of the entire population.

Conclusions: Our data suggests that lower peripheral levels of IGF-1 could be associated with a higher incidence of delirium among elderly patients. Further

prospective studies with larger sample sizes are needed to investigate the association between peripheral levels of IGF-1 and delirium.

Keywords: Biomarker, Delirium, Elderly, IGF-1, Meta-analysis

1. Introduction

Delirium, which clinically presents with impairment in cognition, consciousness, psychomotor behavior, and attention (Ely et al., 2001), may manifest with a wide range of subtypes ranging between hyperactive and hypoactive conditions (Steiner, 2011). Clinically, it usually presents with a sudden onset, which then fluctuates between hours and days and is generally a reversible condition (Yudofsky & Hales, 2008). Etiologically, delirium indicates an organic decline in cerebral function resulting from variable mechanisms. For example, the etiology of alcohol-withdrawal delirium differs from that causing postoperative delirium (Steiner, 2011). Incidence of delirium varies depending on the purpose of investigation. Incidence of delirium varies between 9% and 43% among geriatric patients hospitalized for variable medical conditions (Laurila, Pitkala, Strandberg, & Tilvis, 2002; O'Keeffe & Gosney, 1997). Delirium is commonly observed in elderly patients post surgery, and the incidence of postoperative delirium (POD) ranges widely between 10% and 65% (Radtke et al., 2010; Rudolph & Marcantonio, 2011). Delirium is a serious neuropsychiatric condition with a substantial impact owing to increased morbidity and mortality, high healthcare costs and prolonged hospitalization associated with it (Hustey, Meldon, Smith, & Lex, 2003; Meagher et al., 2007). Regarding mortality rates, reportedly, delirious patients show an overall hazard ratio of 1.9 in elderly

patients in a meta-analysis study (Witlox et al., 2010). Given the inadequate understanding of its multifactorial aetiopathogenesis (Hughes, Patel, & Pandharipande, 2012), researchers are interested in studying the etiology of delirium to better predict its course and prognosis in clinical settings. Although previous reviews (Khan, Zawahiri, Campbell, & Boustani, 2011) have demonstrated the limited role of biomarkers in detection of delirium, researchers have been trying to identify specific biomarkers linked to this condition such as insulin growth factor-1 (IGF-1).

IGF-1 is a member of the IGF family with 70 amino acid peptides, and is primarily produced in the central nervous system (CNS) and peripheral tissues such as the liver (Le Roith, 2003; Torres-Aleman, 2010). IGF-1 in the CNS plays a vital role in enhancing neuronal survival, differentiation, synaptogenesis, and recovery from neural injury (D'Ercole, Ye, & O'Kusky, 2002). IGF-I blocks apoptosis in damaged neurons via several mechanisms, such as delay of apoptosis via activation of PI3K/Akt kinase and Ras/Raf/MEK/ERK pathways and results in long-term survival (Gluckman et al., 1998; Parrizas & LeRoith, 1997; Peruzzi et al., 1999). Clinically, studies have explored its neuroprotective role and association with neurocognitive disorders such as Alzheimer's disease (AD), of which is involved with delirium (Kooijman, Sarre, Michotte, & De Keyser, 2009; Lackey, Gray, & Henricks, 2000). Additionally, IGF-1 deficiency in humans may cause growth abnormalities, including

a smaller sized brain and mental retardation (Werner & LeRoith, 2014). Furthermore, it has been reported that serum IGF-1 levels positively correlate with cognitive performance in healthy elderly subjects (Al-Delaimy, von Muhlen, & Barrett-Connor, 2009; Aleman et al., 2000).

Moreover, as researchers keenly investigating the association between peripheral levels of IGF-1 and delirium, several studies have explored the significance of this correlation in patients undergoing surgery or those with acute medical illnesses (Adamis et al., 2009; Adamis et al., 2007; Cerejeira, Batista, Nogueira, Vaz-Serra, & Mukaetova-Ladinska, 2013; Egberts et al., 2015; Lemstra, Kalisvaart, Vreeswijk, van Gool, & Eikelenboom, 2008; Morandi et al., 2011; Wilson, Broadhurst, Diver, Jackson, & Mottram, 2005). While some studies report that lower peripheral levels of IGF-I could significantly increase the incidence of delirium (Cerejeira et al., 2013; Egberts et al., 2015; Morandi et al., 2011; Wilson et al., 2005), the opposite findings have also been reported by some others (Adamis et al., 2009; Adamis et al., 2007; Lemstra et al., 2008). Possible factors accounting for this discrepancy are inconsistency between recruited patients, such as postoperative or medically ill cases in terms of study designs or clinical status. Thus, the association between peripheral levels of IGF-I and incidence of delirium in a clinical setting needs to be further studied. Given these aforementioned gaps existing in literature, we performed a

comprehensive systematic review and meta-analysis investigating the association between peripheral levels of IGF-1 and delirium, specifically focusing on clinical status of patients. In addition to exploring the difference in this association between surgical or medically ill patients, we also attempted to determine possible factors affecting the correlation between delirium and IGF-1 levels.

2. Materials and methods

Our systematic review and meta-analysis was based on Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000) (supplemental table S1) and was approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB: B-105-12). Two investigators (DJ Li and CS Chu) independently performed database searches, study selection, data extraction, and rating of the methodological quality of included studies. Disagreements between investigators were resolved thorough consensus.

2.1. Database searches

PubMed, Embase, ScienceDirect, ClinicalKey, Cochrane Library, ClinicalTrials.gov and ProQuest were systematically searched from the time of their

inception until October 2nd, 2017. Keywords used for our search included "(IGF OR IGF1 protein OR inflammation mediators OR insulin-like growth factor OR cytokine) AND (delirium OR acute confusion OR consciousness disturbance)" without any limitation about language. Detailed search strings used for the electronic database search and results are shown in the supplemental figure S1.

2.2. Eligibility Criteria and Study Selection

Eligibility criteria applied were: (1) case-control studies comparing peripheral IGF-1 levels between delirious patients and non-delirious controls, or cohorts with detailed baseline data and subsequent delirium risk; (2) those with a diagnosis of delirium based on the definite diagnostic systems or scales, such as confusion assessment method (CAM) (Inouye et al., 1990), the diagnostic and statistical manual of mental disorders, 3rd revision (American Psychiatric Association. 1980) and text-revision (DSM-IV-TR) (American Psychiatric Association. 2000), or Delirium observation screening scale (Schuurmans, Shortridge-Baggett, & Duursma, 2003), Richmond agitation-sedation scale (Sessler et al., 2002); (3) those in whom detailed methods for detecting peripheral IGF-1 were available; and (4) formal registered trials or formal published peer-reviewed articles.

Exclusion criteria were: (1) studies without adequate non-delirious controls; (2)

articles without relation to the comparisons of peripheral IGF-1 levels in delirious patients and controls; (3) those irrelevant to delirium; (4) review articles/commentary articles/case reports/letter to editor; or (5) non-clinical trials in human.

2.3. Methodological Quality Assessment

The modified Newcastle-Ottawa Scale (NOS) was used to rate methodological quality of included studies (Wells GA). This scale considers three domains: selection of participants (maximum of four stars), comparability of groups (maximum of two stars), and measurement (maximum of three stars). Scores ranged from 0 (the lowest) to 9 (the highest), and a score equal to 7 indicated high methodological quality.

2.4. Data Extraction

A predetermined data extraction list was used to extract data for this meta-analysis. To be specific, the extracted data included basic characteristics of participants (mean age and percentage of female), mini-mental status examination (MMSE), and duration of hospitalization.

2.5. Meta-analysis

The primary outcomes were the difference in peripheral IGF-1 levels in delirious patients compared to control groups who did not develop delirium in each recruited

study (calculated as Hedges' *g* statistic). We did not choose difference in means as effect sizes (ESs) of our primary outcome due to presumed different units used among each study. For studies in which peripheral levels of IGF-1 were not available, outcomes were chosen as odd ratios (ORs) (Morandi et al., 2011; Wilson et al., 2005), or only a *p* value (Adamis et al., 2007) according to manuals of Comprehensive Meta-Analysis version 3.0. When peripheral levels of IGF-1 were not available in the included studies, we tried to contact the authors of such studies on at least two separate occasions to try and obtain additional raw data. Additionally, we converted ORs into ES using the formula suggested by the Cochrane Handbook (Higgins & Green, 2011) and derived ES using other statistical parameters such as the *t* or *p* value with the sample size when raw data were not available via email inquiry. We defined an ES and Hedges' *g* less than 0 as "lower peripheral IGF-1 levels in patients with delirium than in controls without delirium". Statistical significance was set as a two-tailed p value < 0.05. All meta-analytical procedures were performed using the Comprehensive Meta-Analysis version 3 (CMA ver. 3.0) (Biostat, Englewood, NJ) software. Meta-analyses were performed using random-effects models due to the anticipated heterogeneity across studies. Briefly, random-effects modeling is more stringent and therefore more convincing than fixed-effects modeling and incorporates a between-study variance in the calculations (Borenstein, Hedges, Higgins, &

Rothstein, 2010).

2.6. Heterogeneity, publication bias, sensitivity test, and meta-regression

We used the Cochran's Q test and the corresponding *p* value to investigate potential heterogeneity among recruited studies (Higgins & Thompson, 2002). The I^2 metric was used to investigate the proportion of variance between recruited studies (Borenstein, Higgins, Hedges, & Rothstein, 2017). The publication bias was determined by visual examination of funnel plots in situations of less than 10 studies (Higgins & Green, 2011) and using thorough Egger's regression analysis if there were more than 10 studies (Egger, Davey Smith, Schneider, & Minder, 1997). In situation of significant publication bias, we arranged Duval and Tweedie`s trim and fill test to adjust the results of meta-analysis (Duval & Tweedie, 2000). Additionally, we performed sensitivity testing with one study removal test to investigate potential confounding by any one of the outlier in the recruited studies, which had been widely used in meta-analysis (Tobias, 1999). Additionally, we performed meta-regression analysis using an unrestricted maximum likelihood method to explore potential moderators. Variables considered for meta-regression analyses were: mean age, female gender (%), MMSE score, and a total modified NOS scores. The meta-regression procedure was only performed when moderator variables were

available from more than 5 individual datasets.

3. Results

3.1. Studies included in the meta-analysis

The whole search picture was depicted as figure 1 and supplemental figure S1. In brief, eighty-two articles enter the full-texts investigation stage, and seventy-two were excluded for specific reasons (see supplemental table S2). Finally, ten articles met our inclusion criteria (Adamis et al., 2007; Cerejeira et al., 2013; Chu et al., 2016; Cinar et al., 2014; Egberts et al., 2015; Lemstra et al., 2008; Morandi et al., 2011; Shen, Shao, Chen, & Guo, 2016; Wilson et al., 2005; Yen et al., 2016). Peripheral levels of IGF-1 were obtained before delirium occurring in the seven studies (Cerejeira et al., 2013; Chu et al., 2016; Cinar et al., 2014; Lemstra et al., 2008; Shen et al., 2016; Wilson et al., 2005; Yen et al., 2016). The participants in other three studies might be drawn IGF-1during delirious status (Adamis et al., 2007; Egberts et al., 2015; Morandi et al., 2011).

3.2. Methodological quality assessment

The mean modified NOS score was 7.4 with standard deviation (SD) = 0.5 across

the ten studies. The score in each domain of the modified NOS is shown in supplemental table S3.

3.3. The main results of the meta-analysis comparing the levels of IGF-1 in patients with delirium and those without delirium

Our systematic review and meta-analysis included 10 articles that met our inclusion criteria. Peripheral (serum or plasma) IGF-1 levels were measured in these ten studies. The quantitative determination of IGF-1 were taken from plasma (Cerejeira et al., 2013; Wilson et al., 2005) and serum (Adamis et al., 2007; Chu et al., 2016; Cinar et al., 2014; Egberts et al., 2015; Morandi et al., 2011; Shen et al., 2016; Yen et al., 2016), respectively. One study (Lemstra et al., 2008) mentioned that IGF-1 was assessed from blood sample (table 1). We found 294 delirious patients (mean age 73.0 years, women 51.0 %) and 604 non-delirious patients (mean age 76.9 years, women 53.2 %) among the 10 studies. Peripheral levels of IGF-1 in patients with delirium were significantly lower than in those without delirium (Hedges' g = -0.209, 95% confidence interval (CI) = -0.393 to -0.026, p = 0.025] (Figure 2) with significant heterogeneity (Q value = 20.215, degree of freedom (df) = 9, I^2 = 55.479%, p = 0.017) but no significant publication bias based on Egger's test [t value = 1.060, df = 8, p = 0.320].

3.3.1. Sensitivity test

The significant result of current meta-analysis became non-significant after removal of the datasets by Adamis, D. (2007) (Hedges' g = -0.184, 95% CI = -0.374 to 0.006, p = 0.058) (Adamis et al., 2007), Egberts, A. (2015) (Hedges' g = -0.175, 95% CI = -0.362 to 0.011, p = 0.066) (Egberts et al., 2015), Shen, H. (2016) (Hedges' g = -0.125, 95% CI = -0.262 to 0.012, p = 0.073) (Shen et al., 2016), or Yen, T.E. (2016) (Hedges' g = -0.193, 95% CI = -0.390 to 0.004, p = 0.055) (Yen et al., 2016).

3.3.2 Meta-regression

There was no any significant association between the differences of peripheral IGF-1 and clinical variables, including percentage of cognitive impairment (p=0.960), mean age (p=0.978), female proportion (p=0.721), mean MMSE scores (p=0.929), or quality of methodology as total modified NOS scores (p=0.270).

4. Discussion

To the best of our knowledge, the study is the first meta-analysis to address the association between peripheral IGF-1 and delirium and suggests that lower peripheral IGF-1 levels were found in patients with delirium compared with those without

delirium. Although causality of delirium and peripheral levels of IGF-1 has yet to be clarified, our study offers additional evidence supporting the immune-inflammatory hypothesis in delirium.

The link between delirium and peripheral levels of IGF-1 can be mediated by cytokines released during inflammatory processes. Reportedly, a strong correlation is seen to exist between delirium and inflammation (Broadhurst & Wilson, 2001). Peripheral IGF-1 can cross the blood-brain barrier and play a role in neuronal function (Reinhardt & Bondy, 1994). It has been reported that administration of IGF-1 reduces secondary neuronal loss after transient neural injuries (Gluckman et al., 1998; Trejo, Carro, Garcia-Galloway, & Torres-Aleman, 2004). Similarly, replacement therapy with IGF-1 ameliorates diabetic neuropathy (Schmidt et al., 1999). Our study provides additional evidence to support this hypothesis. Lower peripheral levels of IGF-1 may possess lesser neuroprotective properties that is anti-apoptotic and anti-inflammatory actions, and contributed higher risk of delirium.

Another factor involved in the connection between peripheral levels of IGF-1 and delirium may be relatively high mean age (almost above 70 years old) of participants in the included studies. Ageing, resulting from increased natural immunity activity, is a low level inflammatory status (Godbout & Johnson, 2009; Licastro et al., 2005).

Inflammation is related to several morbid conditions in the elderly such as cardiovascular disease (Pai et al., 2004) or Alzheimer's disease (Casserly & Topol, 2004). Furthermore, inflammation may result in the breakdown of the blood-brain barrier (Jeppsson et al., 1981) and decrease cholinergic transfer(Hammond, Meador, Aung-Din, & Wilder, 1987). Taken together, elevated levels of proinflammatory cytokine levels have been suggested to predispose the development of delirium in elderly, which is interpreted by the concept of immunosenescence (Godbout & Johnson, 2006). IGF-1, involving neuro-inflammation in the CNS (Trejo et al., 2004), may be also affected by ageing, be associated with delirium. However, our meta-regression showed that mean age did not significantly involve the relation between delirium and IGF-1. In addition to limited case numbers, relatively narrowing distribution of mean age may also restrict the statistical significance. Previous study also indicated that older patients undergoing cardiovascular surgery may develop delirium easily (Cinar et al., 2014). However, clearly more research is required to better understand this issue.

It has been reported that IGF-1 levels positively correlate with cognitive performance in healthy elderly subjects (Al-Delaimy et al., 2009; Aleman et al., 2000). A meta-analysis has reported a significantly positive correlation between IGF-I and cognition in a healthy elderly population (Arwert, Deijen, & Drent, 2005). Another

study concluded that the IGFI levels showed an inverse correlation with cognitive dysfunction (Murialdo et al., 2001). In the present meta-analysis study, only two studies enrolled participants with baseline cognitive healthy, which was defined as an MMSE score of ≧ 24 or excluded when enrollment, and reported that lower peripheral levels of IGF-1 associated with incident of delirium in one study (adjusted Odd ratios [aORs] = 2.52, 95% CI = 1.19 to 5.43, p = 0.019)(Shen et al., 2016) but not another (aORs = 0.99, 95% CI = 0.96 to 1.01, p = 0.183) (Yen et al., 2016). For participants with baseline cognitive impairment, six (Adamis et al., 2007; Cerejeira et al., 2013; Chu et al., 2016; Cinar et al., 2014; Lemstra et al., 2008; Morandi et al., 2011) out of eight (Adamis et al., 2007; Cerejeira et al., 2013; Chu et al., 2016; Cinar et al., 2014; Egberts et al., 2015; Lemstra et al., 2008; Morandi et al., 2011; Wilson et al., 2005) studies showed no significant differences between peripheral levels of IGF-1 and delirium. Therefore, cognitive impairment could be a possible confounder unfavorably affecting the association between delirium and peripheral levels of IGF-1. However, our meta-regression showed that baseline MMSE scores were not significantly linked to a correlation between delirium and IGF-1. This difference may be due to variable statistical methodology between dichotomous grouping [normal cognition vs. mild cognitive impairment (MCI) or dementia] and continuous variables of baseline MMSE scores. The fact that a limited number of cases were studied might

contribute to the insignificance observed with respect to baseline MMSE scores. Furthermore, some studies report that IGF-I levels were unaltered or increased among dementia patients (Nasman et al., 1995; Sara et al., 1982; Tham et al., 1993). A greater number of studies will need to be performed in future to investigate the correlation between cognition and IGF-1 to explore this inconsistency.

Limitations of our study that need to be addressed are: 1) Studying a limited number of cases might be a confounding factor impacting the significance of outcomes. 2) Higher mean age would restrict the application of our findings to younger adults or adolescents. 3) We could not perform subgroup analyses comparing IGF-1 levels in different delirious classifications or diagnostic criteria (hypoactive vs hyperactive delirium and only CAM vs CAM plus DSM-III or -IV diagnosis) due to not enough studies. Future research is required to understand if this influences the relationship observed. 4) Peripheral levels of IGF-1 do not actually reflect the brain levels, and thus the pathogenesis between CNS levels of IGF-1and incident delirium need to be addressed in future studies.

5. Conclusion

In conclusion, lower peripheral levels of IGF-1 appear to be associated with

delirium among elderly patients. Further studies involving a greater number of participants and wider ranges of age would help to investigate the etiology and association between these two entities in future. Studies including more baseline variables and more specific description of diagnosing method to delirium could help us investigate more covariates and conduct subgroup analysis.

Conflict of Interest

The authors state that there are no any competing interests in the current literature.

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Figure legends:

Figure 1. Flow chart showing the selection strategy and inclusion/exclusion criteria employed in our current meta-analysis.

Figure 2. Forest plot of results of pooled effect sizes (Hedges' *g*) and 95% confidence intervals (CIs) from pooled results of peripheral levels of insulin growth factor-1 (IGF-1) between delirious and non-delirious patients within the entire population.

Abbreviation: CI: confidence interval; IGF-1: insulin-like growth factor-1

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Table 1

Summarization of recruited studies in current meta-analysis

Author (year)	Criteria	Population or setting	Delirium / Non-delirium	Mean age	Female (%)	Source	IGF (ng/mL)	Country
Yen, T. E. (2016)	CAM + DSM-IV	Elective knee arthroplasty	22 / 76	73.4±5.1	52.0	serum	57.0±18.6 / 68.4±31.6	USA
Shen, H. (2016)	CAM + DSM-IV	Open abdominal surgery	36 / 104	70.1±6.4	57.2	serum	50.4±16.2 / 67.0±24.1	China
Chu, C. S. (2016)	CAM + DSM-IV	Orthopedic surgery	23 / 80	81.7±4.0	26.2	serum	97.1±47.4 / 96.1±47.6	Taiwan
Egberts, A.	DOSS +	Internal and geriatric ward	23	82.6	53.5	serum	*48.1±32.1	Netherland

(2015)	DSM-IV		63			71.0±43.5	
Cinar, M. A.			15	64.2±10.		1.44±1.76	
	DSM-IV	Cardiovascular surgery			25.7 serum		Turkey
(2014)			20	3		1.03±1.18	
Cerejeira, J.	CAM +		37			*138.3±57.8	
		Elective hip arthroplasty		73.0±6.3	50.5 plasma		Portugal
(2013)	DSM-IV		64			128.2±59.6	
Morandi, A.	CAM +	Critically ill mechanically ventilated	86				
				65	48.2 serum	#n/a	USA
(2011)	CAM-ICU	patients	24				
Lemstra, A.							
	CAM +		18			*109.9	
W.		Acute or elective hip surgery		78.9	69.1 blood		Netherland
	DSM-IV		50			98.4	
(2008)							
Adamis, D.	CAM	Elderly medical unit	22	84.6±6.6	67.1 serum	55.8±33.7	UK

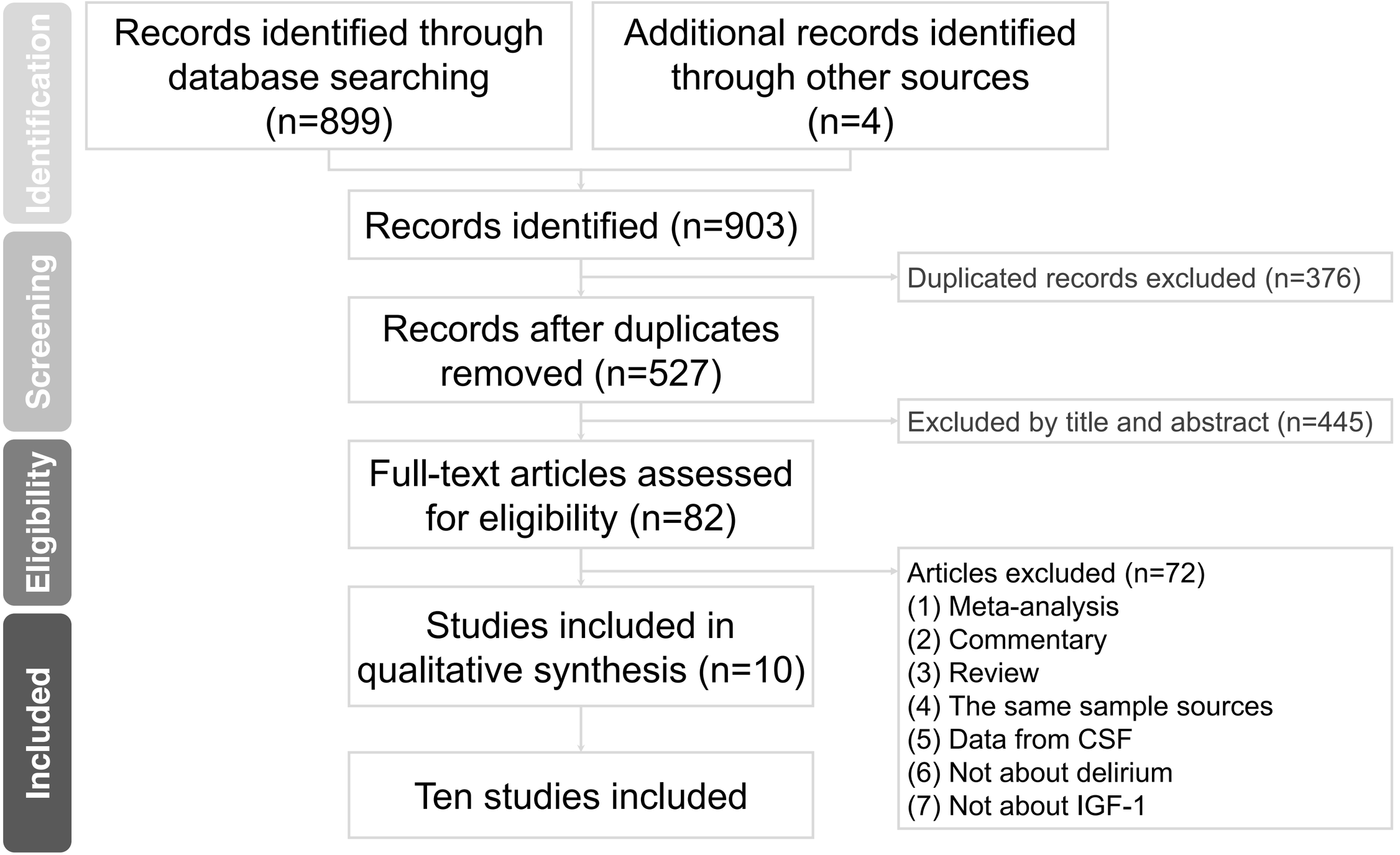
(2007)			35			75.2±33.7
Wilson, K. (2005)	CAM + DSM-III	Acute medical ward	12 88	84.5±4.2	69.0 plasma	[#]n/a UK

[*]: nmol/L convert to ng/ml x 7.63

[#]: derived effect sizes from other statistical parameters

Abbreviation: CAM: confusion assessment method; DOSS: Delirium observation screening scale; ELISA: enzyme-linked immunosorbent assay; IGF: insulin-like growth factor; n/a: not available; RASS: Richmond agitation-sedation scale; RIA: radioimmunoassay; UK: United Kingdom; USA: United States of America.

Figure


Identification
Screening
Eligibility
Included
Records identified through database searching (n=899)
Additional records identified through other sources (n=4)
Records identified (n=903)
Duplicated records excluded (n=376)
Records after duplicates removed (n=527)
Excluded by title and abstract (n=445)
Full-text articles assessed for eligibility (n=82)
Articles excluded (n=72)
(1) Meta-analysis
(2) Commentary
(3) Review
(4) The same sample sources
(5) Data from CSF
(6) Not about delirium
(7) Not about IGF-1
Studies included in qualitative synthesis (n=10)
Ten studies included

Figure

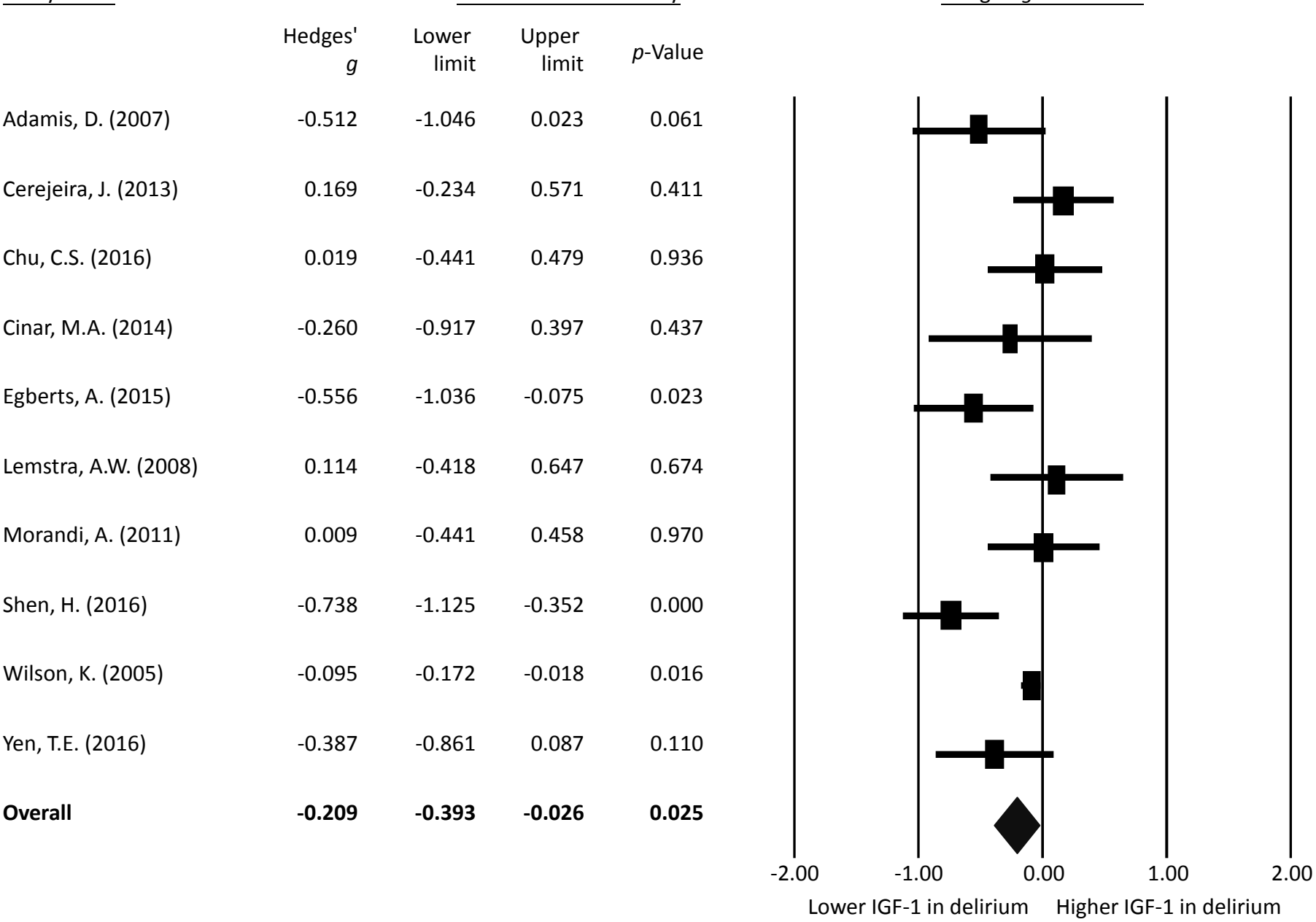


Figure 2 Forest plot of results of pooled effect sizes of recruited studies

table

Table 1

Summarization of recruited studies in current meta-analysis

Author (year)	Criteria	Population or setting	Delirium Non-delirium	Mean age	Female (%)	Source	IGF (ng/mL)	Country
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Chu, C. S. (2016)	CAM + DSM-IV	Orthopedic surgery	23 80	81.7±4.0	26.2	serum	97.1±47.4 96.1±47.6	Taiwan
Egberts, A. (2015)	DOSS + DSM-IV	Internal and geriatric ward	23 63	82.6	53.5	serum	*48.1±32.1 71.0±43.5	Netherland
Cinar, M. A. (2014)	DSM-IV	Cardiovascular surgery	15 20	64.2±10.3	25.7	serum	1.44±1.76 1.03±1.18	Turkey
Cerejeira, J. (2013)	CAM + DSM-IV	Elective hip arthroplasty	37 64	73.0±6.3	50.5	plasma	*138.3±57.8 128.2±59.6	Portugal
Morandi, A. (2011)	CAM + CAM-ICU	Critically ill mechanically ventilated patients	86 24	65	48.2	serum	#n/a	USA
Lemstra, A. W. (2008)	CAM + DSM-IV	Acute or elective hip surgery	18 50	78.9	69.1	blood	*109.9 98.4	Netherland
Adamis, D.	CAM	Elderly medical unit	22	84.6±6.6	67.1	serum	55.8±33.7	UK

(2007)			35			75.2±33.7
Wilson, K. (2005)	CAM + DSM-III	Acute medical ward	12 88	84.5±4.2	69.0 plasma	[#]n/a UK

[*]: nmol/L convert to ng/ml x 7.63

[#]: derived effect sizes from other statistical parameters

Abbreviation: CAM: confusion assessment method; DOSS: Delirium observation screening scale; ELISA: enzyme-linked immunosorbent assay; IGF: insulin-like growth factor; n/a: not available; RASS: Richmond agitation-sedation scale; RIA: radioimmunoassay; UK: United Kingdom; USA: United States of America.

Supplemental table S1: MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	6-7
2	Hypothesis statement	6-7
3	Description of study outcome(s)	6-7
4	Type of exposure or intervention used	N/A
5	Type of study designs used	6-7
6	Study population	6-7
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	8-9
8	Search strategy, including time period included in the synthesis and key words	8-9
9	Effort to include all available studies, including contact with authors	8-9
10	Databases and registries searched	8-10
11	Search software used, name and version, including special features used (eg, explosion)	N/A
12	Use of hand searching (eg, reference lists of obtained articles)	8-10
13	List of citations located and those excluded, including justification	Table 1, supplemental table S2
14	Method of addressing articles published in languages other than English	8-10
15	Method of handling abstracts and unpublished studies	8-10
16	Description of any contact with authors	8-10, acknowledgement
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	9-11
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	9-11
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	9-11
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	9-11
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	9-11
22	Assessment of heterogeneity	9-11
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	9-11
24	Provision of appropriate tables and graphics	Table 1, Figure 2
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2
26	Table giving descriptive information for each study included	Table 1, table 2
27	Results of sensitivity testing (eg, subgroup analysis)	12-15

28	Indication of statistical uncertainty of findings	12-15
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	16-17
30	Justification for exclusion (eg, exclusion of non-English language citations)	16-17 supplementary table S2
31	Assessment of quality of included studies	16-17, supplementary table S3
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	21
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	21
34	Guidelines for future research	21
35	Disclosure of funding source	22

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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Supplemental table S2: Excluded studies and reason

Meta-analysis (n=1)

Shi, C., Yang, C., Gao, R. and Yuan, W. (2015). Risk Factors for Delirium After Spinal Surgery: A Meta-Analysis. World Neurosurgery, 84, 1466-1472.

Commentary (n=1)

Motosko, C., Brown, K. and Kwatra, M. (2012). Insulin-like growth factor 1 and delirium. Int Psychogeriatr, 24, 1872; author reply 1872-1873.

Review (n=18)

Adamis, D. and Meagher, D. (2011). Insulin-like growth factor I and the pathogenesis of delirium: a review of current evidence. J Aging Res, 2011, 951403.

Benhamou, D. and Brouquet, A. (2016). Postoperative cerebral dysfunction in the elderly: Diagnosis and prophylaxis. Journal of Visceral Surgery, 153, S27-S32.

Cerejeira, J., Firmino, H., Vaz-Serra, A. and Mukaetova-Ladinska, E. B. (2010). The neuroinflammatory hypothesis of delirium. Acta Neuropathol, 119, 737-754.

Cerejeira, J., Lagarto, L. and Mukaetova-Ladinska, E. B. (2014). The immunology of delirium. Neuroimmunomodulation, 21, 72-78.

Cunningham, C. and MacLullich, A. M. J. (2013). At the extreme end of the psychoneuroimmunological spectrum: Delirium as a maladaptive sickness behaviour response. Brain, Behavior, and Immunity, 28, 1-13.

de Rooij, S. E., van Munster, B. C., Korevaar, J. C. and Levi, M. (2007). Cytokines and acute phase response in delirium. Journal of Psychosomatic Research, 62, 521-525.

Fong, T. G., Davis, D., Growdon, M. E., Albuquerque, A. and Inouye, S. K. (2015). The interface between delirium and dementia in elderly adults. The Lancet Neurology, 14, 823-832.

Gaudreau, J.-D., Gagnon, P., Roy, M.-A., Harel, F. and Tremblay, A. (2005). Association Between Psychoactive Medications and Delirium in Hospitalized Patients: A Critical Review. Psychosomatics, 46, 302-316.

Gunther, M. L., Morandi, A. and Ely, E. W. (2008). Pathophysiology of Delirium in the Intensive Care Unit. Critical Care Clinics, 24, 45-65.

Khan, B. A., Zawahiri, M., Campbell, N. L. and Boustani, M. A. (2011). Biomarkers for delirium--a review. J Am Geriatr Soc, 59 Suppl 2, S256-261.

LeGrand, S. B. (2012). Delirium in Palliative Medicine: A Review. Journal of Pain and Symptom Management, 44, 583-594.

Maldonado, J. R. (2008). Pathoetiological Model of Delirium: a Comprehensive Understanding of the Neurobiology of Delirium and an Evidence-Based Approach to Prevention and Treatment. Critical Care Clinics, 24, 789-856.

Maldonado, J. R. (2017). Acute Brain Failure: Pathophysiology, Diagnosis, Management, and Sequelae of Delirium. Critical Care Clinics, 33, 461-519.

Marcantonio, E. R., Rudolph, J. L., Culley, D., Crosby, G., Alsop, D. and Inouye, S. K. (2006). Serum biomarkers for delirium. J Gerontol A Biol Sci Med Sci, 61, 1281-1286.

Hall, R. J., Shenkin, S. D. and Maclullich, A. M. (2011). A systematic literature review of cerebrospinal fluid biomarkers in delirium. Dement Geriatr Cogn Disord, 32, 79-93.

Haymore, J. B. and Patel, N. (2016). Delirium in the Neuro Intensive Care Unit. Critical Care Nursing Clinics of North America, 28, 21-35.

Rizk, P., Morris, W., Oladeji, P. and Huo, M. (2016). Review of Postoperative Delirium in Geriatric Patients Undergoing Hip Surgery. Geriatr Orthop Surg Rehabil, 7, 100-105.

Simone, M. J. and Tan, Z. S. (2011). The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. CNS Neurosci Ther, 17, 506-513.

The same sample sources (n=4)

Adamis, D., et al. (2009). Cytokines and IGF-I in delirious and non-delirious acutely ill older medical inpatients. Age Ageing, 38, 326-332; discussion 251.--> *Same population from Adamis, D., Treloar, A., Martin, F. C., Gregson, N., Hamilton, G. and Macdonald, A. J. (2007). APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry, 22, 688-694.*

Adamis, D., Treloar, A., Gregson, N., Macdonald, A. J. and Martin, F. C. (2011). Delirium and the functional recovery of older medical inpatients after acute illness: the significance of biological factors. Arch Gerontol Geriatr, 52, 276-280. --> *Same population from Adamis, D., Treloar, A., Martin, F. C., Gregson, N., Hamilton, G. and Macdonald, A. J. (2007). APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry, 22, 688-694.*

Adamis, D., et al. (2014). Phenomenological and biological correlates of improved cognitive function in hospitalized elderly medical inpatients. Arch Gerontol Geriatr, 59, 593-598. --> *Same population from Adamis, D., Treloar, A., Martin, F. C., Gregson, N., Hamilton, G. and Macdonald, A. J. (2007). APOE and cytokines as biological markers for recovery of prevalent delirium in elderly medical inpatients. Int J Geriatr Psychiatry, 22, 688-694.*

Kwatra, M. and Rivelli, S. (2008). Baseline Plasma Igf-1 Levels Relate to Postoperative Delirium in Knee Arthroplasty Patients. Orlando, FL: American Society of Anesthesiologists→ *Same population from Yen, T. E., et al. (2016). Association between Serum IGF-I levels and Postoperative Delirium in Elderly Subjects Undergoing Elective Knee Arthroplasty. Sci Rep, 6, 20736.*

Results from CSF levels of IGF-1 (n=1)

Cape, E., et al. (2014). Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. J Psychosom Res, 77, 219-225.

Not about delirium (n=1)

Cortes, E., et al. (2005). Insulin-like growth factor–1 gene splice variants as markers of muscle damage in levator ani muscle after the first vaginal delivery. American Journal of Obstetrics and Gynecology, 193, 64-70.

No data about IGF-1 (n=46)

Adamis, D., Treloar, A., Darwiche, F. Z., Gregson, N., Macdonald, A. J. and Martin, F. C. (2007). Associations of delirium with in-hospital and in 6-months mortality in elderly medical inpatients. Age Ageing, 36, 644-649.

Beloosesky, Y., Weiss, A., Hershkovitz, A., Hendel, D. and Barak, V. (2011). Serum transforming growth factor beta-1 post hip fracture repair in elderly patients. Cytokine, 54, 56-60.

Burkhart, C. S., et al. (2010). Modifiable and Nonmodifiable Risk Factors for Postoperative Delirium After Cardiac Surgery With Cardiopulmonary Bypass. Journal of Cardiothoracic and Vascular Anesthesia, 24, 555-559.

Burkhart, C. S., et al. (2014). Effect of n-3 fatty acids on markers of brain injury and incidence of sepsis-associated delirium in septic patients. Acta Anaesthesiol Scand, 58, 689-700.

Capri, M., et al. (2014). Pre-Operative, High-IL-6 Blood Level is a Risk Factor of Post-Operative Delirium Onset in Old Patients. Front Endocrinol (Lausanne), 5, 173.

Cerejeira, J., Nogueira, V., Luis, P., Vaz-Serra, A. and Mukaetova-Ladinska, E. B. (2012). The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc, 60, 669-675.

Chen, W., et al. (2017). Prevalence and risk factors for postoperative delirium in total joint arthroplasty patients: A prospective study. General Hospital Psychiatry, 46, 55-61.

Chen, X.-W., Shi, J.-W., Yang, P.-S. and Wu, Z.-Q. (2014). Preoperative plasma leptin levels predict delirium in elderly patients after hip fracture surgery. Peptides, 57, 31-35.

Fan, Y.-X., et al. (2014). Comparison of restrictive and liberal transfusion strategy on postoperative delirium in aged patients following total hip replacement: A preliminary study. Archives of Gerontology and Geriatrics, 59, 181-185.

Hall, R. J., et al. (2013). Delirium and Cerebrospinal Fluid S100B in Hip Fracture Patients: A Preliminary Study. The American Journal of Geriatric Psychiatry, 21, 1239-1243.

Hall, R. J., et al. (2015). Cerebrospinal fluid cortisol and cytokines in delirium after hip fracture. Psychoneuroendocrinology, 61, 49.

Jackson, T. A., Sheehan, B., Maclullich, A. M., Gladman, J. R. and Lord, J. M. (2014). O2.02: Serum markers of inflammation and abnormalities of the HPA axis are not associated with poor outcome in delirium. European Geriatric Medicine, 5, Supplement 1, S55.

Jalleh, R., Koh, K., Choi, B., Liu, E., Maddison, J. and Hutchinson, M. R. (2012). Role of microglia and toll-like receptor 4 in the pathophysiology of delirium. Medical Hypotheses, 79, 735-739.

Kazmierski, J., Banys, A., Latek, J., Bourke, J. and Jaszewski, R. (2014). Raised IL-2 and TNF-alpha concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. Int Psychogeriatr, 26, 845-855.

Kazmierski, J., et al. (2014). Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. Dement Geriatr Cogn Disord, 38, 65-78.

Li, G., Lei, X., Ai, C., Li, T. and Chen, Z. (2017). Low plasma leptin level at admission predicts delirium in critically ill patients: A prospective cohort study. Peptides, 93, 27-32.

Lin, S.-M., et al. (2008). Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients. Journal of Critical Care, 23, 372-379.

Liu, P., et al. (2013). High serum interleukin-6 level is associated with increased risk of delirium in elderly patients after noncardiac surgery: a prospective cohort study. Chin Med J (Engl), 126, 3621-3627.

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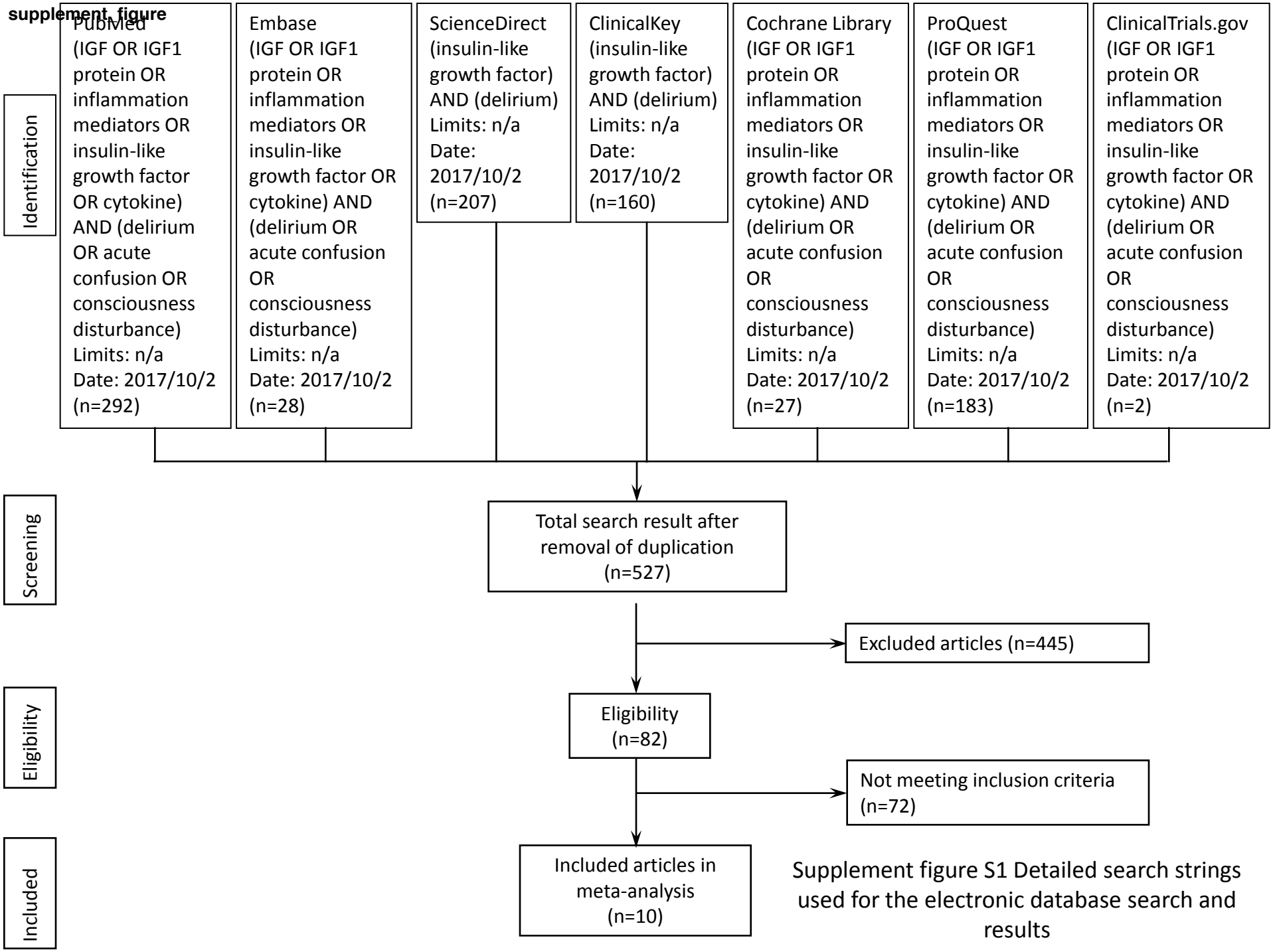
Supplemental Table S3: Newcastle-Ottawa Quality Assessment Scale (NOS) scores of included studies

Author (year)	Selection	Comparability	Outcome	Total scores
Yen, T. E. (2016)	4	2	2	8
Shen, H. (2016)	4	2	1	7
Chu, C. S. (2016)	4	1	2	7
Egberts, A. (2015)	4	2	2	8
Cinar, M. A. (2014)	4	1	2	7
Cerejeira, J. (2013)	4	1	2	7
Morandi, A. (2011)	4	2	2	8
Lemstra, A. W. (2008)	4	1	2	7
Adamis, D. (2007)	4	2	2	8
Wilson, K. (2005)	4	2	1	7



Supplement figure S1 Detailed search strings used for the electronic database search and results