

1 **Low peripheral levels of insulin growth factor-1 are associated with high**
2 **incidence of delirium among elderly patients: A systematic review and**
3 **meta-analysis**
4

5
6 *Running title: MA of IGF-1 and delirium*
7

8
9 Dian-Jeng Li^{a,b,#}, Ping-Tao Tseng^{c,#}, Brendon Stubbs^{d,e,f}, Tien-Yu Chen^{g,h}, Pao-Yen
10 Lin^{i,j}, Shiou-Lan Chen^b, Trevor Thompson^k, Dimitrios Adamis^{l,m}, Che-Sheng Chu^{n,o,*}
11
12
13
14
15

16 ^a *Department of Addiction Science, Kaohsiung Municipal Kai-Syuan Psychiatric*
17 *Hospital, Kaohsiung City, Taiwan*
18

19
20 ^b *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University,*
21 *Taiwan*
22
23

24
25 ^c *WinShine Clinics in Specialty of Psychiatry, Kaohsiung City, Taiwan*
26

27
28 ^d *Physiotherapy Department, South London and Maudsley NHS Foundation Trust,*
29 *London, UK*
30

31
32 ^e *Health Service and Population Research Department, Institute of Psychiatry,*
33 *Psychology and Neuroscience (IoPPN), King's College London, De Crespigny Park,*
34 *London, UK*
35
36

37
38 ^f *Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford,*
39 *UK*
40

41
42
43 ^g *Department of Psychiatry, Tri-Service General Hospital; School of Medicine,*
44 *National Defense Medical Center, Taipei, Taiwan*
45

46
47 ^h *Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan*
48

49
50 ⁱ *Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang*
51 *Gung University College of Medicine, Kaohsiung, Taiwan*
52
53

54
55 ^j *Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung*
56 *Memorial Hospital*
57

58
59 ^k *Faculty of Education and Health, University of Greenwich, London SE9 2UG*
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

^l Sligo Mental Health Services Clarion Rd Sligo, Ireland

^m Research and Academic Institute of Athens, Greece

ⁿ Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

^o Center for Geriatric and Gerontology, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

[#] contributed equally as first author

*** Correspondence to:**

Che-Sheng Chu, MD

Department of Psychiatry, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

Address: No. 386, Dazhong 1st Rd., Zuoying Dist., Kaohsiung City 81362, Taiwan

Telephone: 886-7-3422121

Fax: 886-7-3422288

E-mail: youngtzuchi@hotmail.com/cschu@vghks.gov.tw

1 **Abstract:**

2
3
4
5 *Introduction:* Delirium, a serious condition observed in critically ill patients, clinically
6
7
8 presents with impaired cognition and consciousness. The relationship between
9
10
11 delirium and peripheral levels of insulin growth factor-1 (IGF-1) is unclear. Thus we
12
13
14 conducted a meta-analysis to address this issue.
15
16

17
18
19 *Methods:* Seven major electronic databases were searched from inception until
20
21
22 October 2, 2017 to obtain relevant clinical variables to compare the difference in
23
24
25 IGF-1 levels between delirious and non-delirious elderly in-patients. A random effects
26
27
28 meta-analysis was conducted.
29
30

31
32
33 *Results:* We studied 10 articles involving 294 delirious patients (mean age 73.0 years)
34
35
36 and 604 non-delirious patients (mean age 76.9 years). We found that peripheral levels
37
38
39 of IGF-1 in patients with delirium were significantly lower than in those without
40
41
42 delirium (Hedges' $g = -0.209$, 95% confidence interval [CI] = -0.393 to -0.026 , $p =$
43
44
45 0.025). Meta-regression analyses found that no variables such as percentage of
46
47
48 cognitive impairment, mean age, and female proportion contribute to heterogeneity in
49
50
51 terms of the entire population.
52
53

54
55
56 *Conclusions:* Our data suggests that lower peripheral levels of IGF-1 could be
57
58
59 associated with a higher incidence of delirium among elderly patients. Further
60
61
62

1 prospective studies with larger sample sizes are needed to investigate the association
2
3
4 between peripheral levels of IGF-1 and delirium.
5
6
7

8 *Keywords:* Biomarker, Delirium, Elderly, IGF-1, Meta-analysis
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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

1 patients in a meta-analysis study (Witlox et al., 2010). Given the inadequate
2
3
4 understanding of its multifactorial aetiopathogenesis (Hughes, Patel, & Pandharipande,
5
6
7 2012), researchers are interested in studying the etiology of delirium to better predict
8
9
10 its course and prognosis in clinical settings. Although previous reviews (Khan,
11
12
13 Zawahiri, Campbell, & Boustani, 2011) have demonstrated the limited role of
14
15
16 biomarkers in detection of delirium, researchers have been trying to identify specific
17
18
19 biomarkers linked to this condition such as insulin growth factor-1 (IGF-1).
20
21
22
23

24 IGF-1 is a member of the IGF family with 70 amino acid peptides, and is primarily
25
26
27 produced in the central nervous system (CNS) and peripheral tissues such as the liver
28
29
30 (Le Roith, 2003; Torres-Aleman, 2010). IGF-1 in the CNS plays a vital role in
31
32
33 enhancing neuronal survival, differentiation, synaptogenesis, and recovery from
34
35
36 neural injury (D'Ercole, Ye, & O'Kusky, 2002). IGF-I blocks apoptosis in damaged
37
38
39 neurons via several mechanisms, such as delay of apoptosis via activation of
40
41
42 PI3K/Akt kinase and Ras/Raf/MEK/ERK pathways and results in long-term survival
43
44
45 (Gluckman et al., 1998; Parrizas & LeRoith, 1997; Peruzzi et al., 1999). Clinically,
46
47
48 studies have explored its neuroprotective role and association with neurocognitive
49
50
51 disorders such as Alzheimer's disease (AD), of which is involved with delirium
52
53
54 (Kooijman, Sarre, Michotte, & De Keyser, 2009; Lackey, Gray, & Henricks, 2000).
55
56
57 Additionally, IGF-1 deficiency in humans may cause growth abnormalities, including
58
59
60
61
62
63
64
65

1 a smaller sized brain and mental retardation (Werner & LeRoith, 2014). Furthermore,
2
3
4 it has been reported that serum IGF-1 levels positively correlate with cognitive
5
6
7 performance in healthy elderly subjects (Al-Delaimy, von Muhlen, & Barrett-Connor,
8
9
10 2009; Aleman et al., 2000).

11
12
13
14
15 Moreover, as researchers keenly investigating the association between peripheral
16
17
18 levels of IGF-1 and delirium, several studies have explored the significance of this
19
20
21 correlation in patients undergoing surgery or those with acute medical illnesses
22
23
24 (Adamis et al., 2009; Adamis et al., 2007; Cerejeira, Batista, Nogueira, Vaz-Serra, &
25
26
27 Mukaetova-Ladinska, 2013; Egberts et al., 2015; Lemstra, Kalisvaart, Vreeswijk, van
28
29
30 Gool, & Eikelenboom, 2008; Morandi et al., 2011; Wilson, Broadhurst, Diver,
31
32
33
34 Jackson, & Mottram, 2005). While some studies report that lower peripheral levels of
35
36
37 IGF-I could significantly increase the incidence of delirium (Cerejeira et al., 2013;
38
39
40 Egberts et al., 2015; Morandi et al., 2011; Wilson et al., 2005), the opposite findings
41
42
43 have also been reported by some others (Adamis et al., 2009; Adamis et al., 2007;
44
45
46 Lemstra et al., 2008). Possible factors accounting for this discrepancy are
47
48
49 inconsistency between recruited patients, such as postoperative or medically ill cases
50
51
52
53 in terms of study designs or clinical status. Thus, the association between peripheral
54
55
56 levels of IGF-I and incidence of delirium in a clinical setting needs to be further
57
58
59 studied. Given these aforementioned gaps existing in literature, we performed a
60
61
62
63
64
65

1 comprehensive systematic review and meta-analysis investigating the association
2
3
4 between peripheral levels of IGF-1 and delirium, specifically focusing on clinical
5
6
7 status of patients. In addition to exploring the difference in this association between
8
9
10 surgical or medically ill patients, we also attempted to determine possible factors
11
12
13 affecting the correlation between delirium and IGF-1 levels.
14
15
16
17
18
19
20
21

22 **2. Materials and methods**

23
24
25

26
27 Our systematic review and meta-analysis was based on Meta-analysis Of
28
29 Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000)
30
31 (supplemental table S1) and was approved by the Institutional Review Board of the
32
33 Tri-Service General Hospital (TSGHIRB: B-105-12). Two investigators (DJ Li and
34
35
36 CS Chu) independently performed database searches, study selection, data extraction,
37
38
39 and rating of the methodological quality of included studies. Disagreements between
40
41
42
43
44
45
46 investigators were resolved thorough consensus.
47
48
49

50 *2.1. Database searches*

51
52
53

54 PubMed, Embase, ScienceDirect, ClinicalKey, Cochrane Library,
55
56
57
58 ClinicalTrials.gov and ProQuest were systematically searched from the time of their
59
60
61
62
63
64
65

1 inception until October 2nd, 2017. Keywords used for our search included “(IGF OR
2
3
4 IGF1 protein OR inflammation mediators OR insulin-like growth factor OR cytokine)
5
6
7 AND (delirium OR acute confusion OR consciousness disturbance)” without any
8
9
10 limitation about language. Detailed search strings used for the electronic database
11
12
13 search and results are shown in the supplemental figure S1.
14
15
16
17

18 *2.2. Eligibility Criteria and Study Selection*

19
20
21

22 Eligibility criteria applied were: (1) case-control studies comparing peripheral
23
24
25 IGF-1 levels between delirious patients and non-delirious controls, or cohorts with
26
27
28 detailed baseline data and subsequent delirium risk; (2) those with a diagnosis of
29
30
31 delirium based on the definite diagnostic systems or scales, such as confusion
32
33
34 assessment method (CAM) (Inouye et al., 1990), the diagnostic and statistical manual
35
36
37 of mental disorders, 3rd revision (American Psychiatric Association. 1980) and
38
39
40 text-revision (DSM-IV-TR) (American Psychiatric Association. 2000), or Delirium
41
42
43 observation screening scale (Schuurmans, Shortridge-Baggett, & Duursma, 2003),
44
45
46 Richmond agitation-sedation scale (Sessler et al., 2002); (3) those in whom detailed
47
48
49 methods for detecting peripheral IGF-1 were available; and (4) formal registered trials
50
51
52 or formal published peer-reviewed articles.
53
54
55
56
57

58 Exclusion criteria were: (1) studies without adequate non-delirious controls; (2)
59
60
61
62
63
64
65

1 articles without relation to the comparisons of peripheral IGF-1 levels in delirious
2
3
4 patients and controls; (3) those irrelevant to delirium; (4) review articles/commentary
5
6
7 articles/case reports/letter to editor; or (5) non-clinical trials in human.
8
9

10 11 *2.3. Methodological Quality Assessment* 12 13

14
15
16 The modified Newcastle-Ottawa Scale (NOS) was used to rate methodological
17
18
19 quality of included studies (Wells GA). This scale considers three domains: selection
20
21
22 of participants (maximum of four stars), comparability of groups (maximum of two
23
24
25 stars), and measurement (maximum of three stars). Scores ranged from 0 (the lowest)
26
27
28 to 9 (the highest), and a score equal to 7 indicated high methodological quality.
29
30

31 32 33 *2.4. Data Extraction* 34 35 36

37
38 A predetermined data extraction list was used to extract data for this meta-analysis.
39
40
41 To be specific, the extracted data included basic characteristics of participants (mean
42
43
44 age and percentage of female), mini-mental status examination (MMSE), and duration
45
46
47 of hospitalization.
48
49

50 51 52 *2.5. Meta-analysis* 53 54 55

56
57 The primary outcomes were the difference in peripheral IGF-1 levels in delirious
58
59
60 patients compared to control groups who did not develop delirium in each recruited
61
62
63
64
65

1 study (calculated as Hedges' *g* statistic). We did not choose difference in means as
2
3
4 effect sizes (ESs) of our primary outcome due to presumed different units used among
5
6
7 each study. For studies in which peripheral levels of IGF-1 were not available,
8
9
10 outcomes were chosen as odd ratios (ORs) (Morandi et al., 2011; Wilson et al., 2005),
11
12
13 or only a *p* value (Adamis et al., 2007) according to manuals of Comprehensive
14
15
16 Meta-Analysis version 3.0. When peripheral levels of IGF-1 were not available in the
17
18
19 included studies, we tried to contact the authors of such studies on at least two
20
21
22 separate occasions to try and obtain additional raw data. Additionally, we converted
23
24
25 ORs into ES using the formula suggested by the Cochrane Handbook (Higgins &
26
27
28 Green, 2011) and derived ES using other statistical parameters such as the *t* or *p* value
29
30
31 with the sample size when raw data were not available via email inquiry. We defined
32
33
34 an ES and Hedges' *g* less than 0 as "lower peripheral IGF-1 levels in patients with
35
36
37 delirium than in controls without delirium". Statistical significance was set as a
38
39
40 two-tailed *p* value < 0.05. All meta-analytical procedures were performed using the
41
42
43 Comprehensive Meta-Analysis version 3 (CMA ver. 3.0) (Biostat, Englewood, NJ)
44
45
46 software. Meta-analyses were performed using random-effects models due to the
47
48
49 anticipated heterogeneity across studies. Briefly, random-effects modeling is more
50
51
52 stringent and therefore more convincing than fixed-effects modeling and incorporates
53
54
55 a between-study variance in the calculations (Borenstein, Hedges, Higgins, &
56
57
58
59
60
61
62
63
64
65

1 Rothstein, 2010).

2
3
4
5 *2.6. Heterogeneity, publication bias, sensitivity test, and meta-regression*
6
7

8
9 We used the Cochran's Q test and the corresponding p value to investigate potential
10
11 heterogeneity among recruited studies (Higgins & Thompson, 2002). The I^2 metric
12
13 was used to investigate the proportion of variance between recruited studies
14
15
16
17
18 (Borenstein, Higgins, Hedges, & Rothstein, 2017). The publication bias was
19
20
21
22 determined by visual examination of funnel plots in situations of less than 10 studies
23
24
25 (Higgins & Green, 2011) and using thorough Egger's regression analysis if there were
26
27
28 more than 10 studies (Egger, Davey Smith, Schneider, & Minder, 1997). In situation
29
30
31 of significant publication bias, we arranged Duval and Tweedie's trim and fill test to
32
33
34
35 adjust the results of meta-analysis (Duval & Tweedie, 2000). Additionally, we
36
37
38 performed sensitivity testing with one study removal test to investigate potential
39
40
41 confounding by any one of the outlier in the recruited studies, which had been widely
42
43
44 used in meta-analysis (Tobias, 1999). Additionally, we performed meta-regression
45
46
47 analysis using an unrestricted maximum likelihood method to explore potential
48
49
50 moderators. Variables considered for meta-regression analyses were: mean age,
51
52
53 female gender (%), MMSE score, and a total modified NOS scores. The
54
55
56
57 meta-regression procedure was only performed when moderator variables were
58
59
60

1 available from more than 5 individual datasets.
2
3
4
5
6
7
8

9 **3. Results**

10 *3.1. Studies included in the meta-analysis*

11
12
13
14
15
16
17
18 The whole search picture was depicted as figure 1 and supplemental figure S1. In
19 brief, eighty-two articles enter the full-texts investigation stage, and seventy-two were
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

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-1 during delirious status (Adamis et al., 2007; Egberts et al., 2015; Morandi et al., 2011).

54 *3.2. Methodological quality assessment*

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

1 the ten studies. The score in each domain of the modified NOS is shown in
2
3
4 supplemental table S3.
5
6
7

8 *3.3. The main results of the meta-analysis comparing the levels of IGF-1 in patients*
9
10
11 *with delirium and those without delirium*
12
13
14
15

16 Our systematic review and meta-analysis included 10 articles that met our inclusion
17
18
19 criteria. Peripheral (serum or plasma) IGF-1 levels were measured in these ten studies.
20
21
22 The quantitative determination of IGF-1 were taken from plasma (Cerejeira et al.,
23
24
25 2013; Wilson et al., 2005) and serum (Adamis et al., 2007; Chu et al., 2016; Cinar et
26
27
28 al., 2014; Egberts et al., 2015; Morandi et al., 2011; Shen et al., 2016; Yen et al.,
29
30
31 2016), respectively. One study (Lemstra et al., 2008) mentioned that IGF-1 was
32
33
34 assessed from blood sample (table 1). We found 294 delirious patients (mean age 73.0
35
36
37 years, women 51.0 %) and 604 non-delirious patients (mean age 76.9 years, women
38
39
40 53.2 %) among the 10 studies. Peripheral levels of IGF-1 in patients with delirium
41
42
43 were significantly lower than in those without delirium (Hedges' $g = -0.209$, 95%
44
45
46 confidence interval (CI) = -0.393 to -0.026 , $p = 0.025$] (Figure 2) with significant
47
48
49 heterogeneity (Q value = 20.215, degree of freedom (df) = 9, $I^2 = 55.479\%$, $p = 0.017$)
50
51
52 but no significant publication bias based on Egger's test [t value = 1.060, df = 8, $p =$
53
54
55
56
57 0.320].
58
59
60
61
62
63
64
65

1 *3.3.1. Sensitivity test*

2
3
4
5 The significant result of current meta-analysis became non-significant after
6
7
8 removal of the datasets by Adamis, D. (2007) (Hedges' $g = -0.184$, 95% CI = -0.374
9
10
11 to 0.006, $p = 0.058$) (Adamis et al., 2007), Egberts, A. (2015) (Hedges' $g = -0.175$,
12
13
14 95% CI = -0.362 to 0.011, $p = 0.066$) (Egberts et al., 2015), Shen, H. (2016) (Hedges'
15
16
17 $g = -0.125$, 95% CI = -0.262 to 0.012, $p = 0.073$) (Shen et al., 2016), or Yen, T.E.
18
19
20
21 (2016) (Hedges' $g = -0.193$, 95% CI = -0.390 to 0.004, $p = 0.055$) (Yen et al., 2016).
22
23
24

25 *3.3.2 Meta-regression*

26
27
28
29
30 There was no any significant association between the differences of peripheral
31
32
33 IGF-1 and clinical variables, including percentage of cognitive impairment ($p=0.960$),
34
35
36 mean age ($p=0.978$), female proportion ($p=0.721$), mean MMSE scores ($p=0.929$), or
37
38
39 quality of methodology as total modified NOS scores ($p=0.270$).
40
41
42
43
44
45
46
47

48 **4. Discussion**

49
50
51
52
53 To the best of our knowledge, the study is the first meta-analysis to address the
54
55
56 association between peripheral IGF-1 and delirium and suggests that lower peripheral
57
58
59 IGF-1 levels were found in patients with delirium compared with those without
60

1 delirium. Although causality of delirium and peripheral levels of IGF-1 has yet to be
2
3
4 clarified, our study offers additional evidence supporting the immune-inflammatory
5
6
7 hypothesis in delirium.
8
9

10
11 The link between delirium and peripheral levels of IGF-1 can be mediated by
12
13 cytokines released during inflammatory processes. Reportedly, a strong correlation is
14
15 seen to exist between delirium and inflammation (Broadhurst & Wilson, 2001).
16
17

18
19 Peripheral IGF-1 can cross the blood-brain barrier and play a role in neuronal function
20
21 (Reinhardt & Bondy, 1994). It has been reported that administration of IGF-1 reduces
22
23 secondary neuronal loss after transient neural injuries (Gluckman et al., 1998; Trejo,
24
25 Carro, Garcia-Galloway, & Torres-Aleman, 2004). Similarly, replacement therapy
26
27 with IGF-1 ameliorates diabetic neuropathy (Schmidt et al., 1999). Our study provides
28
29 additional evidence to support this hypothesis. Lower peripheral levels of IGF-1 may
30
31 possess lesser neuroprotective properties that is anti-apoptotic and anti-inflammatory
32
33 actions, and contributed higher risk of delirium.
34
35
36
37
38
39
40
41
42
43
44
45
46

47
48 Another factor involved in the connection between peripheral levels of IGF-1 and
49
50 delirium may be relatively high mean age (almost above 70 years old) of participants
51
52 in the included studies. Ageing, resulting from increased natural immunity activity, is
53
54 a low level inflammatory status (Godbout & Johnson, 2009; Licastro et al., 2005).
55
56
57
58
59
60
61
62
63
64
65

1 Inflammation is related to several morbid conditions in the elderly such as
2
3
4 cardiovascular disease (Pai et al., 2004) or Alzheimer's disease (Casserly & Topol,
5
6
7 2004). Furthermore, inflammation may result in the breakdown of the blood-brain
8
9
10 barrier (Jeppsson et al., 1981) and decrease cholinergic transfer(Hammond, Meador,
11
12
13 Aung-Din, & Wilder, 1987). Taken together, elevated levels of proinflammatory
14
15
16 cytokine levels have been suggested to predispose the development of delirium in
17
18
19 elderly, which is interpreted by the concept of immunosenescence (Godbout &
20
21
22 Johnson, 2006). IGF-1, involving neuro-inflammation in the CNS (Trejo et al., 2004),
23
24
25 may be also affected by ageing, be associated with delirium. However, our
26
27
28 meta-regression showed that mean age did not significantly involve the relation
29
30
31 between delirium and IGF-1. In addition to limited case numbers, relatively
32
33
34 narrowing distribution of mean age may also restrict the statistical significance.
35
36
37 Previous study also indicated that older patients undergoing cardiovascular surgery
38
39
40 may develop delirium easily (Cinar et al., 2014). However, clearly more research is
41
42
43 required to better understand this issue.
44
45
46

47
48
49 It has been reported that IGF-1 levels positively correlate with cognitive
50
51
52 performance in healthy elderly subjects (Al-Delaimy et al., 2009; Aleman et al., 2000).
53
54
55 A meta-analysis has reported a significantly positive correlation between IGF-I and
56
57
58 cognition in a healthy elderly population (Arwert, Deijen, & Drent, 2005). Another
59
60
61

1 study concluded that the IGFI levels showed an inverse correlation with cognitive
2
3
4 dysfunction (Murialdo et al., 2001). In the present meta-analysis study, only two
5
6
7 studies enrolled participants with baseline cognitive healthy, which was defined as an
8
9
10 MMSE score of ≥ 24 or excluded when enrollment, and reported that lower
11
12
13 peripheral levels of IGF-1 associated with incident of delirium in one study (adjusted
14
15
16 Odd ratios [aORs] = 2.52, 95% CI = 1.19 to 5.43, $p = 0.019$)(Shen et al., 2016) but
17
18
19 not another (aORs = 0.99, 95% CI = 0.96 to 1.01, $p = 0.183$) (Yen et al., 2016). For
20
21
22 participants with baseline cognitive impairment, six (Adamis et al., 2007; Cerejeira et
23
24
25 al., 2013; Chu et al., 2016; Cinar et al., 2014; Lemstra et al., 2008; Morandi et al.,
26
27
28 2011) out of eight (Adamis et al., 2007; Cerejeira et al., 2013; Chu et al., 2016; Cinar
29
30
31 et al., 2014; Egberts et al., 2015; Lemstra et al., 2008; Morandi et al., 2011; Wilson et
32
33
34 al., 2005) studies showed no significant differences between peripheral levels of
35
36
37 IGF-1 and delirium. Therefore, cognitive impairment could be a possible confounder
38
39
40 unfavorably affecting the association between delirium and peripheral levels of IGF-1.
41
42
43
44 However, our meta-regression showed that baseline MMSE scores were not
45
46
47 significantly linked to a correlation between delirium and IGF-1. This difference may
48
49
50
51 be due to variable statistical methodology between dichotomous grouping [normal
52
53
54 cognition vs. mild cognitive impairment (MCI) or dementia] and continuous variables
55
56
57
58 of baseline MMSE scores. The fact that a limited number of cases were studied might
59
60
61
62
63
64
65

1 contribute to the insignificance observed with respect to baseline MMSE scores.
2
3
4 Furthermore, some studies report that IGF-I levels were unaltered or increased among
5
6
7 dementia patients (Nasman et al., 1995; Sara et al., 1982; Tham et al., 1993). A greater
8
9
10 number of studies will need to be performed in future to investigate the correlation
11
12
13 between cognition and IGF-1 to explore this inconsistency.
14
15

16
17 Limitations of our study that need to be addressed are: 1) Studying a limited
18
19 number of cases might be a confounding factor impacting the significance of
20
21
22 outcomes. 2) Higher mean age would restrict the application of our findings to
23
24
25 younger adults or adolescents. 3) We could not perform subgroup analyses comparing
26
27
28 IGF-1 levels in different delirious classifications or diagnostic criteria (hypoactive vs
29
30
31 hyperactive delirium and only CAM vs CAM plus DSM-III or -IV diagnosis) due to
32
33
34 not enough studies. Future research is required to understand if this influences the
35
36
37 relationship observed. 4) Peripheral levels of IGF-1 do not actually reflect the brain
38
39
40 levels, and thus the pathogenesis between CNS levels of IGF-1 and incident delirium
41
42
43 need to be addressed in future studies.
44
45
46
47
48
49
50
51
52
53

54 **5. Conclusion**

55
56
57
58 In conclusion, lower peripheral levels of IGF-1 appear to be associated with
59
60

1 delirium among elderly patients. Further studies involving a greater number of
2
3
4 participants and wider ranges of age would help to investigate the etiology and
5
6
7 association between these two entities in future. Studies including more baseline
8
9
10 variables and more specific description of diagnosing method to delirium could help
11
12
13 us investigate more covariates and conduct subgroup analysis.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Conflict of Interest

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

Acknowledgements

The authors declare that there are no conflicts of interest or funding in relation to the subject of this study.

1 **Figure legends:**
2
3
4

5 **Figure 1.** Flow chart showing the selection strategy and inclusion/exclusion criteria
6
7
8 employed in our current meta-analysis.
9

10
11
12 **Figure 2.** Forest plot of results of pooled effect sizes (Hedges' g) and 95% confidence
13 intervals (CIs) from pooled results of peripheral levels of insulin growth
14 factor-1 (IGF-1) between delirious and non-delirious patients within the
15
16
17
18
19
20
21
22
23 entire population.
24

25
26
27 Abbreviation: CI: confidence interval; IGF-1: insulin-like growth factor-1
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **References:**
2
3
4

5 Adamis, D., Lunn, M., Martin, F. C., Treloar, A., Gregson, N., Hamilton, G., &
6
7 Macdonald, A. J. (2009). Cytokines and IGF-I in delirious and non-delirious
8
9 acutely ill older medical inpatients. *Age Ageing*, 38(3), 326-332.
10
11
12 Adamis, D., Treloar, A., Martin, F. C., Gregson, N., Hamilton, G., & Macdonald, A.
13
14 J. (2007). APOE and cytokines as biological markers for recovery of prevalent
15
16 delirium in elderly medical inpatients. *Int J Geriatr Psychiatry*, 22(7),
17
18 688-694.
19
20
21 Al-Delaimy, W. K., von Muhlen, D., & Barrett-Connor, E. (2009). Insulinlike growth
22
23 factor-1, insulinlike growth factor binding protein-1, and cognitive function in
24
25 older men and women. *J Am Geriatr Soc*, 57(8), 1441-1446.
26
27
28 Aleman, A., de Vries, W. R., de Haan, E. H., Verhaar, H. J., Samson, M. M., &
29
30 Koppeschaar, H. P. (2000). Age-sensitive cognitive function, growth hormone
31
32 and insulin-like growth factor 1 plasma levels in healthy older men.
33
34 *Neuropsychobiology*, 41(2), 73-78.
35
36
37 American Psychiatric Association. (1980). *Diagnostic and Statistical Manual of*
38
39 *Mental Disorder* (3rd ed., text rev.). Washington, DC: American Psychiatric
40
41 Association.
42
43
44 American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of*
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 *Mental Disorder* (4th ed., text rev.). Washington, DC: American Psychiatric
2
3
4 Association.

5
6
7 Arwert, L. I., Deijen, J. B., & Drent, M. L. (2005). The relation between insulin-like
8
9
10 growth factor I levels and cognition in healthy elderly: a meta-analysis.
11
12
13 *Growth Horm IGF Res*, 15(6), 416-422.

14
15
16 Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic
17
18
19 introduction to fixed-effect and random-effects models for meta-analysis. *Res*
20
21
22 *Synth Methods*, 1(2), 97-111.

23
24
25 Borenstein, M., Higgins, J. P., Hedges, L. V., & Rothstein, H. R. (2017). Basics of
26
27
28 meta-analysis: I² is not an absolute measure of heterogeneity. *Res Synth*
29
30
31 *Methods*, 8(1), 5-18.

32
33
34 Broadhurst, C., & Wilson, K. (2001). Immunology of delirium: new opportunities for
35
36
37
38 treatment and research. *Br J Psychiatry*, 179, 288-289.

39
40
41 Casserly, I., & Topol, E. (2004). Convergence of atherosclerosis and Alzheimer's
42
43
44
45 disease: inflammation, cholesterol, and misfolded proteins. *Lancet*, 363(9415),
46
47
48 1139-1146.

49
50
51 Cerejeira, J., Batista, P., Nogueira, V., Vaz-Serra, A., & Mukaetova-Ladinska, E. B.
52
53
54
55 (2013). The stress response to surgery and postoperative delirium: evidence of
56
57
58 hypothalamic-pituitary-adrenal axis hyperresponsiveness and decreased
59
60

1 suppression of the GH/IGF-1 Axis. *J Geriatr Psychiatry Neurol*, 26(3),
2
3
4 185-194.
5

6
7 Chu, C. S., Liang, C. K., Chou, M. Y., Lin, Y. T., Hsu, C. J., Chu, C. L., & Chou, P.
8
9
10 H. (2016). Lack of Association between Pre-Operative Insulin-Like Growth
11
12 Factor-1 and the Risk of Post-Operative Delirium in Elderly Chinese Patients.
13
14
15
16
17 *Psychiatry Investig*, 13(3), 327-332.
18

19
20 Cinar, M. A., Balikci, A., Sertoglu, E., Mehmet, A. K., Serdar, M. A., & Ozmenler,
21
22
23 K. N. (2014). Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology.
24
25
26
27
28 *Noro Psikiyatrs Ars*, 51(4), 376-382.

29
30 D'Ercole, A. J., Ye, P., & O'Kusky, J. R. (2002). Mutant mouse models of insulin-like
31
32 growth factor actions in the central nervous system. *Neuropeptides*, 36(2-3),
33
34
35
36
37 209-220.
38

39 Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of
40
41 testing and adjusting for publication bias in meta-analysis. *Biometrics*, 56(2),
42
43
44
45
46
47 455-463.

48
49 Egberts, A., Wijnbeld, E. H., Fekkes, D., van der Ploeg, M. A., Ziere, G., Hooijkaas,
50
51
52 H., . . . Mattace-Raso, F. U. (2015). Neopterin: a potential biomarker for
53
54
55
56
57 delirium in elderly patients. *Dement Geriatr Cogn Disord*, 39(1-2), 116-124.

58
59 Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in
60
61

1 meta-analysis detected by a simple, graphical test. *BMJ*, 315(7109), 629-634.

2
3
4 Ely, E. W., Inouye, S. K., Bernard, G. R., Gordon, S., Francis, J., May, L., . . . Dittus,
5
6
7 R. (2001). Delirium in mechanically ventilated patients: validity and reliability
8
9
10 of the confusion assessment method for the intensive care unit (CAM-ICU).
11
12
13 *JAMA*, 286(21), 2703-2710.

14
15
16 Gluckman, P. D., Guan, J., Williams, C., Scheepens, A., Zhang, R., Bennet, L., &
17
18
19 Gunn, A. (1998). Asphyxial brain injury--the role of the IGF system. *Mol Cell*
20
21
22 *Endocrinol*, 140(1-2), 95-99.

23
24
25
26 Godbout, J. P., & Johnson, R. W. (2006). Age and neuroinflammation: a lifetime of
27
28
29 psychoneuroimmune consequences. *Neurol Clin*, 24(3), 521-538.

30
31
32 Godbout, J. P., & Johnson, R. W. (2009). Age and neuroinflammation: a lifetime of
33
34
35 psychoneuroimmune consequences. *Immunol Allergy Clin North Am*, 29(2),
36
37
38 321-337.

39
40
41
42 Hammond, E. J., Meador, K. J., Aung-Din, R., & Wilder, B. J. (1987). Cholinergic
43
44
45 modulation of human P3 event-related potentials. *Neurology*, 37(2), 346-350.

46
47
48 Higgins, J. P., & Green, S. (2011). *Cochrane Handbook for Systematic Reviews of*
49
50
51 *Interventions* (5.1.0 ed.): The Cochrane Collaboration. Available from
52
53
54 www.handbook.cochrane.org.

55
56
57
58 Higgins, J. P., & Thompson, S. G. (2002). Quantifying heterogeneity in a
59
60

1 meta-analysis. *Stat Med*, 21(11), 1539-1558.

2
3
4 Hughes, C. G., Patel, M. B., & Pandharipande, P. P. (2012). Pathophysiology of acute
5
6
7 brain dysfunction: what's the cause of all this confusion? *Curr Opin Crit Care*,
8
9
10 18(5), 518-526.

11
12
13 Hustey, F. M., Meldon, S. W., Smith, M. D., & Lex, C. K. (2003). The effect of
14
15
16 mental status screening on the care of elderly emergency department patients.
17
18
19 *Ann Emerg Med*, 41(5), 678-684.

20
21
22 Inouye, S. K., van Dyck, C. H., Alessi, C. A., Balkin, S., Siegal, A. P., & Horwitz, R.
23
24
25
26 I. (1990). Clarifying confusion: the confusion assessment method. A new
27
28
29 method for detection of delirium. *Ann Intern Med*, 113(12), 941-948.

30
31
32 Jeppsson, B., Freund, H. R., Gimmon, Z., James, J. H., von Meyenfeldt, M. F., &
33
34
35
36 Fischer, J. E. (1981). Blood-brain barrier derangement in sepsis: cause of
37
38
39 septic encephalopathy? *Am J Surg*, 141(1), 136-142.

40
41
42 Khan, B. A., Zawahiri, M., Campbell, N. L., & Boustani, M. A. (2011). Biomarkers
43
44
45 for delirium--a review. *J Am Geriatr Soc*, 59 Suppl 2, S256-261.

46
47
48 Kooijman, R., Sarre, S., Michotte, Y., & De Keyser, J. (2009). Insulin-like growth
49
50
51 factor I: a potential neuroprotective compound for the treatment of acute
52
53
54 ischemic stroke? *Stroke*, 40(4), e83-88.

55
56
57
58 Lackey, B. R., Gray, S. L., & Henricks, D. M. (2000). Actions and interactions of the
59
60

1 IGF system in Alzheimer's disease: review and hypotheses. *Growth Horm IGF*
2
3
4 *Res*, 10(1), 1-13.
5

6
7 Laurila, J. V., Pitkala, K. H., Strandberg, T. E., & Tilvis, R. S. (2002). Confusion
8
9
10 assessment method in the diagnostics of delirium among aged hospital
11
12
13 patients: would it serve better in screening than as a diagnostic instrument? *Int*
14
15
16 *J Geriatr Psychiatry*, 17(12), 1112-1119.
17
18

19
20 Le Roith, D. (2003). The insulin-like growth factor system. *Exp Diabesity Res*, 4(4),
21
22
23 205-212.
24
25

26 Lemstra, A. W., Kalisvaart, K. J., Vreeswijk, R., van Gool, W. A., & Eikelenboom, P.
27
28
29 (2008). Pre-operative inflammatory markers and the risk of postoperative
30
31
32 delirium in elderly patients. *Int J Geriatr Psychiatry*, 23(9), 943-948.
33
34
35

36 Licastro, F., Candore, G., Lio, D., Porcellini, E., Colonna-Romano, G., Franceschi,
37
38
39 C., & Caruso, C. (2005). Innate immunity and inflammation in ageing: a key
40
41
42 for understanding age-related diseases. *Immun Ageing*, 2, 8.
43
44

45 Meagher, D. J., Moran, M., Raju, B., Gibbons, D., Donnelly, S., Saunders, J., &
46
47
48 Trzepacz, P. T. (2007). Phenomenology of delirium. Assessment of 100 adult
49
50
51 cases using standardised measures. *Br J Psychiatry*, 190, 135-141.
52
53
54

55 Morandi, A., Gunther, M. L., Pandharipande, P. P., Jackson, J. C., Thompson, J. L.,
56
57
58 Shintani, A. K., . . . Girard, T. D. (2011). Insulin-like growth factor-1 and
59
60

1 delirium in critically ill mechanically ventilated patients: a preliminary
2
3
4 investigation. *Int Psychogeriatr*, 23(7), 1175-1181.
5
6

7 Murialdo, G., Barreca, A., Nobili, F., Rollero, A., Timossi, G., Gianelli, M. V., . . .
8
9

10 Polleri, A. (2001). Relationships between cortisol, dehydroepiandrosterone
11
12 sulphate and insulin-like growth factor-I system in dementia. *J Endocrinol*
13
14 *Invest*, 24(3), 139-146.
15
16
17
18

19 Nasman, B., Olsson, T., Seckl, J. R., Eriksson, S., Viitanen, M., Bucht, G., &
20
21

22 Carlstrom, K. (1995). Abnormalities in adrenal androgens, but not of
23
24 glucocorticoids, in early Alzheimer's disease. *Psychoneuroendocrinology*,
25
26
27
28
29
30
31
32

33 O'Keeffe, S. T., & Gosney, M. A. (1997). Assessing attentiveness in older hospital
34
35 patients: global assessment versus tests of attention. *J Am Geriatr Soc*, 45(4),
36
37
38
39
40
41
42

43 Pai, J. K., Pischon, T., Ma, J., Manson, J. E., Hankinson, S. E., Joshipura, K., . . .
44

45 Rimm, E. B. (2004). Inflammatory markers and the risk of coronary heart
46
47
48
49
50
51
52

53 Parrizas, M., & LeRoith, D. (1997). Insulin-like growth factor-1 inhibition of
54
55
56
57
58
59
60
61
62
63
64
65

apoptosis is associated with increased expression of the bcl-xL gene product.
Endocrinology, 138(3), 1355-1358.

1 Peruzzi, F., Prisco, M., Dews, M., Salomoni, P., Grassilli, E., Romano, G., . . .

2
3
4 Baserga, R. (1999). Multiple signaling pathways of the insulin-like growth
5
6
7 factor 1 receptor in protection from apoptosis. *Mol Cell Biol*, *19*(10),
8
9
10 7203-7215.
11

12
13 Radtke, F. M., Franck, M., MacGuill, M., Seeling, M., Lutz, A., Westhoff, S., . . .

14
15
16 Spies, C. D. (2010). Duration of fluid fasting and choice of analgesic are
17
18
19 modifiable factors for early postoperative delirium. *Eur J Anaesthesiol*, *27*(5),
20
21
22 411-416.
23
24

25
26 Reinhardt, R. R., & Bondy, C. A. (1994). Insulin-like growth factors cross the

27
28
29 blood-brain barrier. *Endocrinology*, *135*(5), 1753-1761.
30
31

32
33 Rudolph, J. L., & Marcantonio, E. R. (2011). Review articles: postoperative delirium:

34
35
36 acute change with long-term implications. *Anesth Analg*, *112*(5), 1202-1211.
37
38

39 Sara, V. R., Hall, K., Enzell, K., Gardner, A., Morawski, R., & Wetterberg, L. (1982).

40
41
42 Somatomedins in aging and dementia disorders of the Alzheimer type.

43
44
45 *Neurobiol Aging*, *3*(2), 117-120.
46
47

48 Schmidt, R. E., Dorsey, D. A., Beaudet, L. N., Plurad, S. B., Parvin, C. A., & Miller,

49
50
51 M. S. (1999). Insulin-like growth factor I reverses experimental diabetic

52
53
54 autonomic neuropathy. *Am J Pathol*, *155*(5), 1651-1660.
55
56
57

58 Schuurmans, M. J., Shortridge-Baggett, L. M., & Duursma, S. A. (2003). The

1 Delirium Observation Screening Scale: a screening instrument for delirium.

2
3
4 *Res Theory Nurs Pract*, 17(1), 31-50.

5
6
7 Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K.

8
9
10 A., . . . Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale:

11
12 validity and reliability in adult intensive care unit patients. *Am J Respir Crit*

13
14
15 *Care Med*, 166(10), 1338-1344.

16
17
18 Shen, H., Shao, Y., Chen, J., & Guo, J. (2016). Insulin-Like Growth Factor-1, a

19
20
21
22 Potential Predicative Biomarker for Postoperative Delirium Among Elderly

23
24
25 Patients with Open Abdominal Surgery. *Curr Pharm Des*, 22(38), 5879-5883.

26
27
28 Steiner, L. A. (2011). Postoperative delirium. Part 1: pathophysiology and risk

29
30
31 factors. *Eur J Anaesthesiol*, 28(9), 628-636.

32
33
34 Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., . .

35
36
37 . Thacker, S. B. (2000). Meta-analysis of observational studies in

38
39
40 epidemiology: a proposal for reporting. Meta-analysis Of Observational

41
42
43 Studies in Epidemiology (MOOSE) group. *JAMA*, 283(15), 2008-2012.

44
45
46
47 Tham, A., Nordberg, A., Grissom, F. E., Carlsson-Skwirut, C., Viitanen, M., & Sara,

48
49
50 V. R. (1993). Insulin-like growth factors and insulin-like growth factor

51
52
53 binding proteins in cerebrospinal fluid and serum of patients with dementia of

54
55
56 the Alzheimer type. *J Neural Transm Park Dis Dement Sect*, 5(3), 165-176.

1 Tobias, A. (1999). Assessing the influence of a single study in meta-analysis. *STATA*
2
3
4 *technical bulletin*, 47, 15–17.
5

6
7 Torres-Aleman, I. (2010). Toward a comprehensive neurobiology of IGF-I. *Dev*
8
9
10 *Neurobiol*, 70(5), 384-396.
11

12
13 Trejo, J. L., Carro, E., Garcia-Galloway, E., & Torres-Aleman, I. (2004). Role of
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

insulin-like growth factor I signaling in neurodegenerative diseases. *J Mol*
Med (Berl), 82(3), 156-162.

Wells GA, S. B., O'Connell D, Peterson J, Welch V, et al.. (2011) The
Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized
studies in meta-analysis. Available:
www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

Werner, H., & LeRoith, D. (2014). Insulin and insulin-like growth factor receptors in
the brain: physiological and pathological aspects. *Eur Neuropsychopharmacol*,
24(12), 1947-1953.

Wilson, K., Broadhurst, C., Diver, M., Jackson, M., & Mottram, P. (2005). Plasma
insulin growth factor-1 and incident delirium in older people. *Int J Geriatr*
Psychiatry, 20(2), 154-159.

Witlox, J., Eurelings, L. S., de Jonghe, J. F., Kalisvaart, K. J., Eikelenboom, P., & van
Gool, W. A. (2010). Delirium in elderly patients and the risk of postdischarge

1 mortality, institutionalization, and dementia: a meta-analysis. *JAMA*, 304(4),
2
3
4 443-451.
5

6
7 Yen, T. E., Allen, J. C., Rivelli, S. K., Patterson, S. C., Metcalf, M. R., Flink, B. J., . .
8

9
10 . Kwatra, M. M. (2016). Association between Serum IGF-I levels and
11
12 Postoperative Delirium in Elderly Subjects Undergoing Elective Knee
13
14 Arthroplasty. *Sci Rep*, 6, 20736.
15
16
17

18
19 Yudofsky, S. C., & Hales, R. E. (2008). *The American Psychiatric Publishing*
20
21 *textbook of neuropsychiatry and behavioral neurosciences* (5th ed.).
22
23
24
25
26 Washington, DC: American Psychiatric Pub.
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49

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

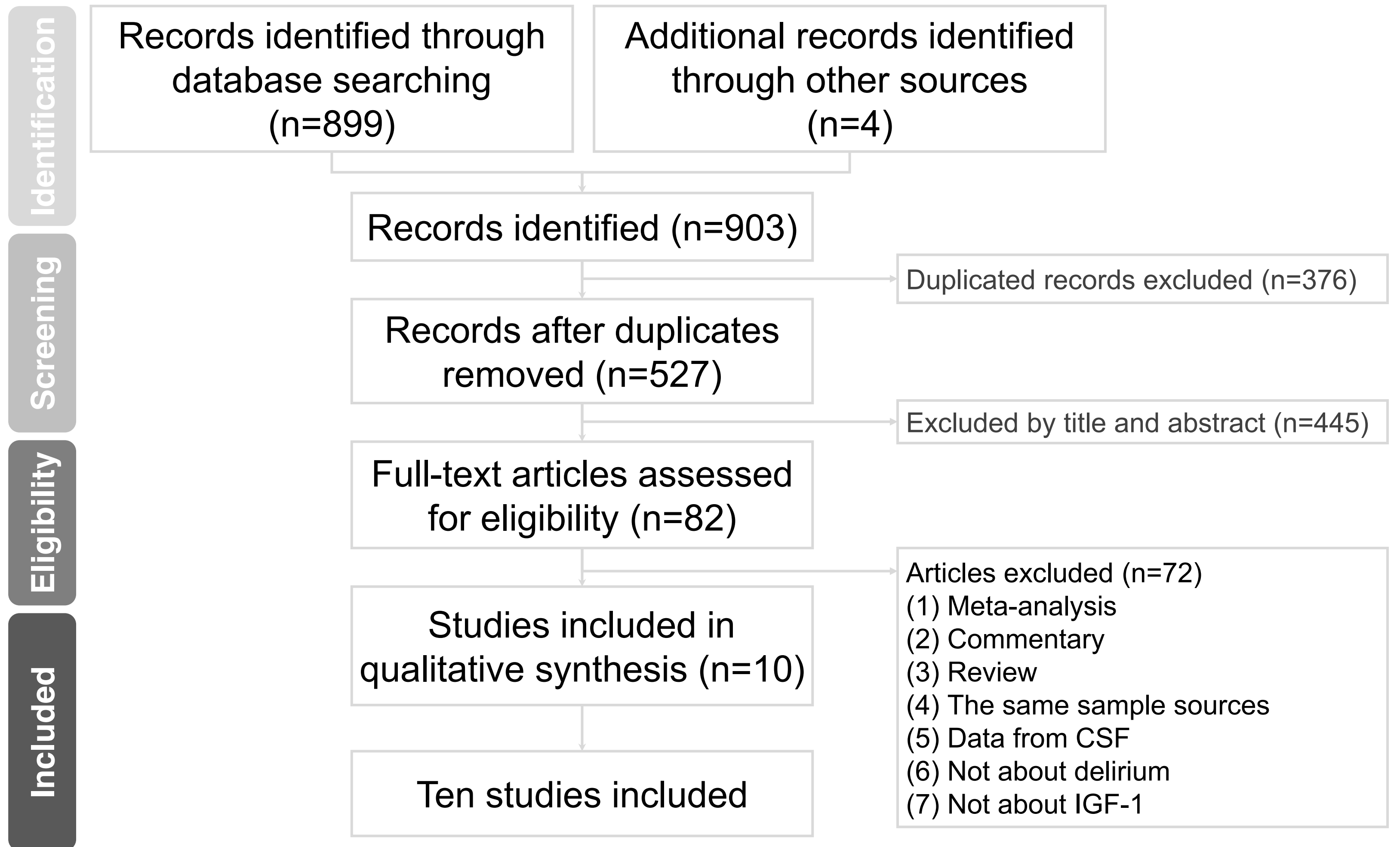
*: nmol/L convert to ng/ml x 7.63

[#]: 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.



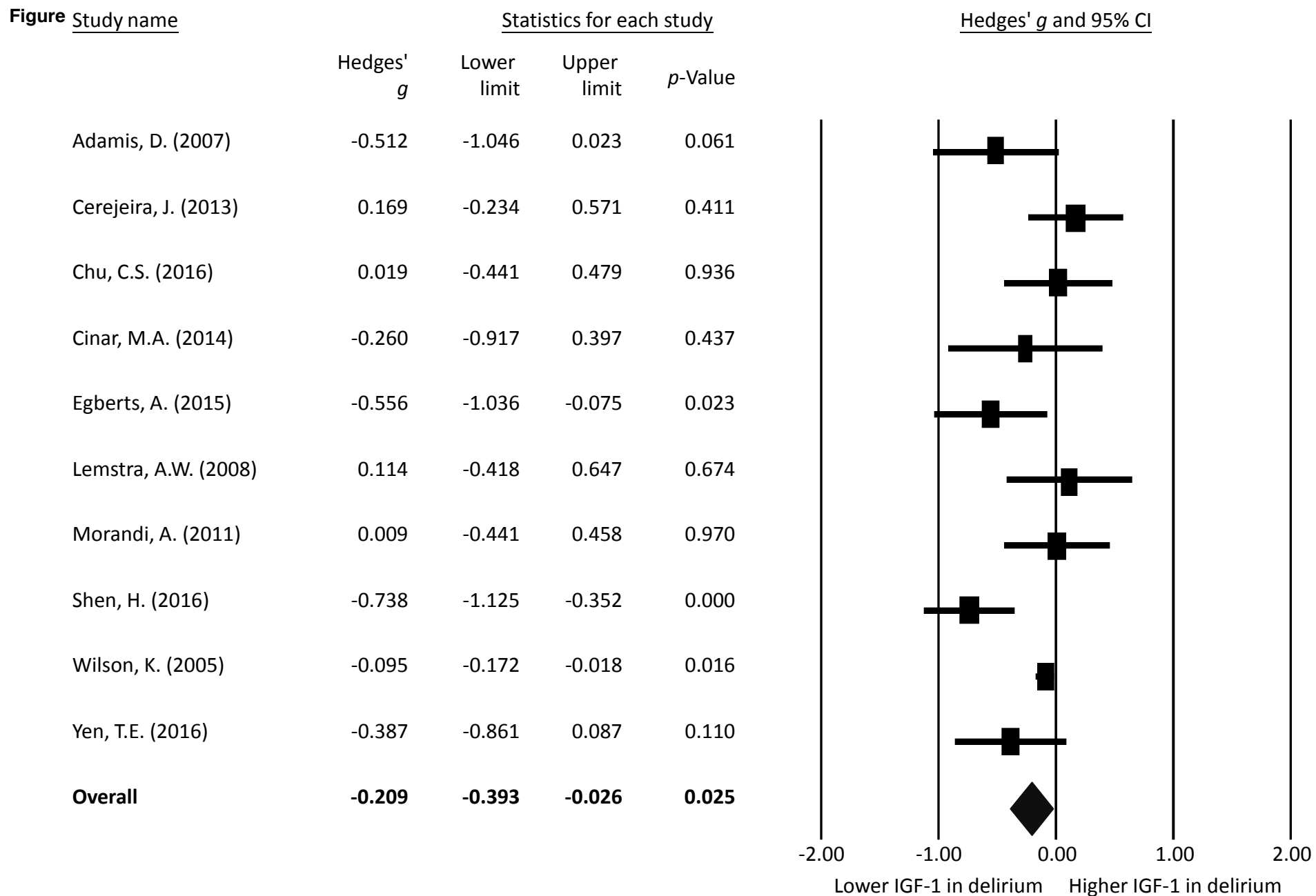


Figure 2 Forest plot of results of pooled effect sizes of recruited studies

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. (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.	CAM +			12			
(2005)	DSM-III	Acute medical ward		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

 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.

Transcribed from the original paper within the NEUROSURGERY® Editorial Office, Atlanta, GA, United States. August 2012.

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 MacLulich, 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 MacLulich, 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., MacLulich, 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.
- Macdonald, A., Adamis, D., Treloar, A., and Martin, F. (2007). C-reactive protein levels predict the incidence of delirium and recovery from it. *Age Ageing*. 2007, 36, 222-5.
- MacLulich, A. M., et al. (2011). Cerebrospinal fluid interleukin-8 levels are higher in people with hip fracture with perioperative delirium than in controls. *J Am Geriatr Soc*, 59, 1151-1153.
- Mariscalco, G., et al. (2012). Preoperative Statin Therapy Is Not Associated With a Decrease in the Incidence of Delirium After Cardiac Operations. *The Annals of Thoracic Surgery*, 93, 1439-1447.
- Morandi, A., et al. (2013). Vitamin D and delirium in critically ill patients: a preliminary investigation. *Journal of Critical Care*, 28, 230-235.
- Mossello, E., et al. (2014). O2.04: Predictors and prognosis of delirium among older subjects in Cardiology Intensive Care Units. *European Geriatric Medicine*, 5, Supplement 1, S55.
- Naeije, G., Depondt, C., Meeus, C., Korpak, K., Pepersack, T. and Legros, B. (2014). EEG patterns compatible with nonconvulsive status epilepticus are common in elderly patients with delirium: a prospective study with continuous EEG monitoring. *Epilepsy & Behavior*, 36, 18-21.
- Neerland, B. E., et al. (2016). Associations Between Delirium and Preoperative Cerebrospinal Fluid C-Reactive Protein, Interleukin-6, and Interleukin-6 Receptor in Individuals with Acute Hip Fracture. *J Am Geriatr Soc*, 64, 1456-1463.
- Ngo, L. H., et al. (2017). Methodologic considerations in the design and analysis of nested case-control studies: association between cytokines and postoperative delirium. *BMC Med Res Methodol*, 17, 88.

- Nguyen, D. N., Huyghens, L., Schiettecatte, J., Smitz, J. and Vincent, J.-L. (2016). High prolactin levels are associated with more delirium in septic patients. *Journal of Critical Care*, 33, 56-61.
- O'Sullivan, R., Inouye, S. K. and Meagher, D. (2014). Delirium and depression: inter-relationship and clinical overlap in elderly people. *The Lancet Psychiatry*, 1, 303-311.
- Pearson, A., et al. (2010). Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls. *BMC Res Notes*, 3, 33.
- Plaschke, K., et al. (2010). Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. *Intensive Care Med*, 36, 2081-2089.
- Rudolph, J. L., et al. (2008). Chemokines are associated with delirium after cardiac surgery. *J Gerontol A Biol Sci Med Sci*, 63, 184-189.
- Schmitt, E. M., et al. (2012). Novel risk markers and long-term outcomes of delirium: the successful aging after elective surgery (SAGES) study design and methods. *J Am Med Dir Assoc*, 13, 818.e811-810.
- Skrede, K., Wyller, T. B., Watne, L. O., Seljeflot, I. and Juliebo, V. (2015). Is there a role for monocyte chemoattractant protein-1 in delirium? Novel observations in elderly hip fracture patients. *BMC Res Notes*, 8, 186.
- Sun, L., et al. (2016). Production of inflammatory cytokines, cortisol, and Abeta1-40 in elderly oral cancer patients with postoperative delirium. *Neuropsychiatr Dis Treat*, 12, 2789-2795.
- Tsang, L. F., et al. (2012). Developing a predictive tool for post-operative delirium in orthopaedic settings in Hong Kong. *International Journal of Orthopaedic and Trauma Nursing*, 16, 147-159.
- Tsuruta, R., et al. (2010). Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. *General Hospital Psychiatry*, 32, 607-611.
- van den Boogaard, M., et al. (2011). Biomarkers associated with delirium in critically ill patients and their relation with long-term subjective cognitive dysfunction; indications for different pathways governing delirium in inflamed and noninflamed patients. *Crit Care*, 15, R297.
- van Munster, B. C., et al. (2010). Cortisol, interleukins and S100B in delirium in the elderly. *Brain and Cognition*, 74, 18-23.
- van Munster, B. C., Korevaar, J. C., Zwinderman, A. H., Levi, M., Wiersinga, W. J. and De Rooij, S. E. (2008). Time-course of cytokines during delirium in elderly patients with hip fractures. *J Am Geriatr Soc*, 56, 1704-1709.
- van Munster, B. C., et al. (2012). Longitudinal assessment of serum anticholinergic activity in delirium of the elderly. *J Psychiatr Res*, 46, 1339-1345.
- van Steijn, J.H., Nieboer, P., Hospers, G.A., de Vries, E.G., and Mulder, N.H. (2001). Delirium after interleukin-2 and alpha-interferon therapy for renal cell carcinoma. *Anticancer Res*, 21, 3699-700.
- Vasunilashorn, S. M., et al. (2015). Cytokines and Postoperative Delirium in Older Patients Undergoing Major Elective Surgery. *J Gerontol A Biol Sci Med Sci*, 70, 1289-1295.

- Westhoff, D., et al. (2013). Preoperative cerebrospinal fluid cytokine levels and the risk of postoperative delirium in elderly hip fracture patients. *J Neuroinflammation*, 10, 122.
- Westhoff, D., et al. (2015). Preoperative protein profiles in cerebrospinal fluid in elderly hip fracture patients at risk for delirium: A proteomics and validation study. *BBA Clinical*, 4, 115-122.
- Zhang, Z., Pan, L., Deng, H., Ni, H. and Xu, X. (2014). Prediction of delirium in critically ill patients with elevated C-reactive protein. *Journal of Critical Care*, 29, 88-92.
- Zhang, Z.-Y., et al. (2016). Impact of length of red blood cells transfusion on postoperative delirium in elderly patients undergoing hip fracture surgery: A cohort study. *Injury*, 47, 408-412.

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

