



STUDY PROTOCOL

# Prospective Investigation of Markers of Elevated Delirium Risk (PRIMED Risk) study protocol: a prospective, observational cohort study investigating blood and cerebrospinal fluid biomarkers for delirium and cognitive dysfunction in older patients [version 1; peer review: awaiting peer review]

Jonathan Whitby <sup>1,2</sup>, Sohail Bampoe<sup>2,3</sup>, James N Fullerton <sup>4</sup>, Ashley Smaje<sup>5</sup>, Joanna Hornby<sup>1</sup>, Bence Hajdu<sup>2,3</sup>, Nick Schofield<sup>6</sup>, Ronnie Stafford<sup>7</sup>, Henrik Zetterberg<sup>8</sup>, Daniel F McAuley <sup>9</sup>, Peter Passmore<sup>10</sup>, Emma Cunningham<sup>10</sup>, John Whittle <sup>11</sup>, David Walker<sup>2,3</sup>, Daniel Davis <sup>1</sup>

<sup>1</sup>MRC Unit for Lifelong Health and Ageing at UCL, University College London, London, UK

<sup>2</sup>Centre for Perioperative Medicine, University College London, London, UK

<sup>3</sup>Department of Anaesthesia and Perioperative Medicine, University College London Hospitals NHS Trust, London, UK

<sup>4</sup>Division of Medicine, University College London, London, UK

<sup>5</sup>University College London Hospitals NHS Trust, London, UK

<sup>6</sup>Department of Anaesthesia, Royal Free Hospital, London, London, UK

<sup>7</sup>Department of Computer Science, University College London, London, UK

<sup>8</sup>UK Dementia Research Institute at UCL, University College London, London, UK

<sup>9</sup>Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Belfast, UK

<sup>10</sup>Centre for Public Health, Queen's University Belfast, Belfast, UK

<sup>11</sup>Department of Anesthesiology, Duke University School of Medicine, Durham, USA

**V1** First published: 08 Jan 2020, 5:5 (<https://doi.org/10.12688/wellcomeopenres.15658.1>)

Latest published: 08 Jan 2020, 5:5 (<https://doi.org/10.12688/wellcomeopenres.15658.1>)

## Abstract

**Background:** Delirium is a common post-operative complication, particularly in older adults undergoing major or emergency procedures. It is associated with increased length of intensive care and hospital stay, post-operative mortality and subsequent dementia risk. Current methods of predicting delirium incidence, duration and severity have limitations. Investigation of blood and cerebrospinal fluid (CSF) biomarkers linked to delirium may improve understanding of the underlying pathophysiology, particularly with regard to the extent this is shared or distinct with underlying dementia. Together, these have the potential for development of better risk stratification tools and perioperative interventions.

**Methods:** 200 patients over the age of 70 scheduled for surgery with routine spinal anaesthetic will be recruited from UK hospitals. Their cognitive and functional baseline status will be assessed pre-operatively by telephone. Time-matched CSF and blood samples will be taken at the time of surgery and analysed for known biomarkers of neurodegeneration and

## Open Peer Review

**Reviewer Status** AWAITING PEER REVIEW

Any reports and responses or comments on the article can be found at the end of the article.

neuroinflammation. Patients will be assessed daily for delirium until hospital discharge and will have regular cognitive follow-up for two years. Primary outcomes will be change in modified Telephone Interview for Cognitive Status (TICS-m) score at 12 months and rate of change of TICS-m score. Delirium severity, duration and biomarker levels will be treated as exposures in a random effects linear regression models. PRIMED Risk has received regulatory approvals from Health Research Authority and London – South East Research Ethics Committee.

**Discussion:** The main anticipated output from this study will be the quantification of biomarkers of acute and chronic contributors to cognitive impairment after surgery. In addition, we aim to develop better risk prediction models for adverse cognitive outcomes.

### Keywords

delirium, epidemiology, biomarkers, prognosis

**Corresponding author:** Jonathan Whitby ([j.whitby@ucl.ac.uk](mailto:j.whitby@ucl.ac.uk))

**Author roles:** **Whitby J:** Data Curation, Investigation, Writing – Original Draft Preparation, Writing – Review & Editing; **Bampoe S:** Funding Acquisition, Investigation, Project Administration, Writing – Review & Editing; **Fullerton JN:** Conceptualization, Investigation, Project Administration, Supervision, Writing – Review & Editing; **Smaje A:** Data Curation, Investigation, Project Administration, Writing – Review & Editing; **Hornby J:** Data Curation, Project Administration, Supervision, Writing – Review & Editing; **Hajdu B:** Investigation, Project Administration, Writing – Review & Editing; **Schofield N:** Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing; **Stafford R:** Methodology, Software, Visualization; **Zetterberg H:** Funding Acquisition, Investigation, Methodology, Validation, Writing – Review & Editing; **McAuley DF:** Funding Acquisition, Methodology, Resources, Validation; **Passmore P:** Funding Acquisition, Methodology, Resources, Validation; **Cunningham E:** Funding Acquisition, Methodology, Resources, Validation; **Whittle J:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Walker D:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Davis D:** Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work is supported by Wellcome [107467]; Dunhill Medical Trust [RPGF1810\91]; and UCLH Biomedical Research Centre.

*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

**Copyright:** © 2020 Whitby J *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**How to cite this article:** Whitby J, Bampoe S, Fullerton JN *et al.* **Prospective Investigation of Markers of Elevated Delirium Risk (PRIMED Risk) study protocol: a prospective, observational cohort study investigating blood and cerebrospinal fluid biomarkers for delirium and cognitive dysfunction in older patients [version 1; peer review: awaiting peer review]** Wellcome Open Research 2020, 5:5 (<https://doi.org/10.12688/wellcomeopenres.15658.1>)

**First published:** 08 Jan 2020, 5:5 (<https://doi.org/10.12688/wellcomeopenres.15658.1>)

## Introduction

Delirium, a neuropsychiatric syndrome characterised by altered arousal, inattention and other cognitive deficits, is a common response to acute physiological stressors. The magnitude of the stress required to precipitate delirium is inversely proportional to the degree of prior brain vulnerability<sup>1</sup>. Delirium is therefore common in acutely ill older people, affecting at least 25% such inpatients at any time<sup>2</sup>, and will frequently complicate perioperative care<sup>3</sup>. The prevalence of postoperative delirium depends on type of surgery, particularly emergency procedures in populations with high frailty or comorbidities, but an overall postoperative incidence of 20% is a reasonable estimate<sup>4</sup>. Elective surgery carries a lower, but still significant risk (4% in a population-based cohort)<sup>5</sup>. Estimated prevalence varies substantially according to detection methods and diagnostic algorithms used<sup>6</sup>. Nonetheless, delirium is consistently associated with a range of adverse outcomes: increased length of stay, admission to critical care, institutionalisation and subsequent cognitive impairment and dementia risk<sup>5,7,8</sup>.

The pathophysiological mechanisms that underpin perioperative delirium and its sequelae have yet to be systematically studied. Certain pathways may account for the development of delirium itself, while others may drive longer-term cognitive outcomes such as progression of dementia<sup>9</sup>. The degree to which these interrelate, are separate or shared is largely unknown. One approach to investigate the neural basis of delirium has been to use cerebrospinal fluid (CSF) samples obtained through regional anaesthesia<sup>10</sup>.

Potential modifiable perioperative risk factors for delirium include depth of anaesthesia, intraoperative hypotension and cerebral oxygenation. These measures have been investigated separately and together in various surgical contexts but have not been extensively correlated with CSF biomarkers and longer-term neurocognitive outcomes<sup>11</sup>.

## Aims

To understand mechanisms underlying perioperative delirium by assessing CSF and blood-based biomarkers of acute and chronic brain injury. Through pre- and post-operative follow-up, the cross-sectional and longitudinal significance of delirium and its biomarkers can be assessed. We will include intra-operative fronto-temporal processed EEG and functional near-infrared spectroscopy with perioperative delirium and subsequent cognitive decline. Together, we envisage these findings will lead to better ways of predicting delirium and long-term cognitive outcomes.

## Objectives

1. Recruit a cohort of individuals aged  $\geq 70$  years undergoing elective and emergency surgery and where neuraxial anaesthesia/analgesia (spinal anaesthesia) is part of the anaesthetic technique.
2. Acquire paired CSF-blood samples to assess systemic inflammatory and neuroinflammatory markers of chronic neurodegeneration and acute brain injury.

3. Assess the impact of common neurophysiological insults in the perioperative period on the incidence of delirium and its sequelae.
4. Undertake serial measures of cognitive function, including delirium, with outcomes ascertained for at least two years.

PRIMED Risk will collaborate closely with investigators from Queen's University Belfast (QUB), which have access to an existing cohort of  $n=282$  CSF samples collected from elective hip and knee replacements (PI: Cunningham)<sup>12</sup>. Our clinical assessment and CSF analysis protocols are closely aligned and we envisage replicating findings across both sets of samples where relevant.

## Hypotheses

1. Biomarkers of acute and chronic brain injury are cumulatively associated with higher incidence of perioperative delirium.
2. Biomarkers of acute and chronic brain injury interact multiplicatively, associated with the fastest degree of cognitive decline.
3. Perioperative physiological stressors such as prolonged hypotension, excessive depth of anaesthesia and cerebral hypoxia are associated with clinical delirium and faster cognitive decline.

## Methods

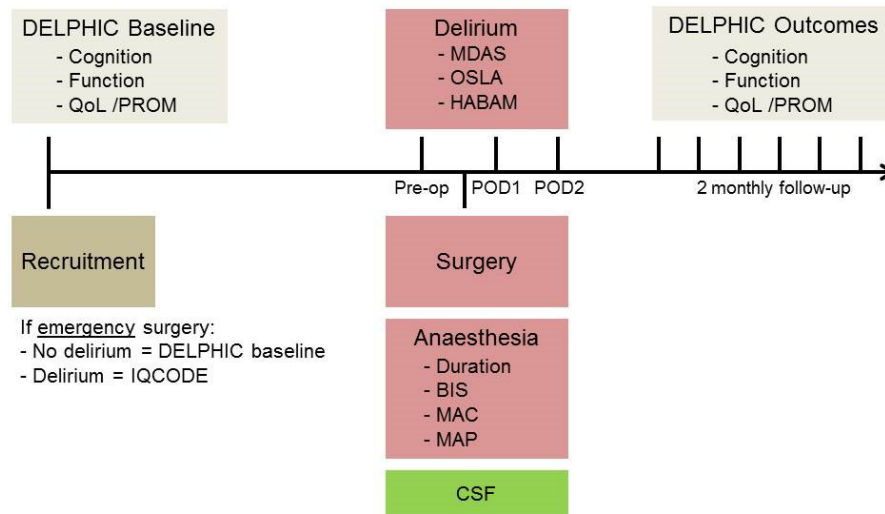
### Recruitment

Adults aged  $\geq 70$  years undergoing surgery with planned spinal anaesthesia will be identified at the time of listing and approached either in person (e.g. at a pre-operative assessment clinic), or by letter. Emergency surgical patients will be identified from emergency theatre lists (Figure 1). Patients will initially be recruited from University College London Hospitals (UCLH) and the Royal Free Hospital (RFH) but other sites may open through the NIHR Clinical Research Network. In addition to the experience of our QUB co-investigators, we have piloted the identification, consent and follow-up of potential participants across both sites using a range of approaches and have shown 25% recruitment to be feasible.

Planned patient groups include urological, colorectal, hepatic and gynae-oncological resections, major vascular surgery and emergency neck of femur fracture repair. Cardiothoracic and neurosurgical patients will be excluded because direct brain complications through routes other than delirium are more likely in these cases. Patients will also be excluded if they are aphasic or do not speak English sufficiently to undertake cognitive assessments, if they were not scheduled to receive spinal anaesthesia as standard of care, or were not expected to survive hospital stay.

### Primary outcome

Modified Telephone Interview for Cognitive Status (TICS-m) score ascertained 12 months after index surgery<sup>13,14</sup>.



**Figure 1.** Schematic showing timing of recruitment, delirium assessments, CSF sampling and follow-up.

#### Pre-operative assessment of baseline function

Enrolled patients will be contacted by telephone prior to admission for surgery to complete a baseline neurocognitive and functional assessment. This includes assessment of general health, subjective memory complaints, hearing, vision, nutrition, continence, falls and mood. Pre-operative function will be assessed using the Barthel Index of Activities of Daily Living and the Nottingham Extended Activities of Daily Living Scale. Cognitive assessments include the Modified Telephone Interview for Cognitive Status (TICS-m), as well as measures of attention, recall, and verbal fluency from the Addenbrooke's Cognitive Examination III (ACE-III). Emergency participants will also be recruited at admission. If such patients do not have delirium, the standard baseline assessment will be applied. For those with prevalent delirium, an additional assessment of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) will be undertaken. This has shown to be a feasible method for obtaining a proxy for estimating a pre-existing dementia in patients with delirium<sup>15</sup>.

#### Peri-operative data collection

Depth of anaesthesia (derived from processed fronto-temporal EEG) and cerebral oxygenation will be monitored with bispectral index (BIS) and near-infrared spectroscopy (NIRS) sensors respectively, attached to the patient prior to anaesthetic induction to monitor changes in these parameters during induction and intubation. Arterial catheters will routinely be used to monitor intra-operative and post-operative blood pressure.

Physiological parameters from the anaesthetic machine monitor will be contemporaneously recorded onto a research laptop at 1-minute intervals for the duration of the surgical procedure. UCLH uses an anaesthetic charting system integrated into the electronic health records system; additional physiological measurements will be extracted from these electronic anaesthetic records. Parameters recorded will include end-tidal carbon dioxide (etCO<sub>2</sub>), minimum alveolar concentration (MAC) if using

inhalational agents, invasive blood pressure, mean arterial pressure (MAP), cardiac output, arterial oxygen saturation (SpO<sub>2</sub>), heart rate and core body temperature.

Case report forms will be used to collect patient information including demographics, body mass index, medical and drug history, functional capacity in metabolic equivalents (METs) and cardiopulmonary exercise test (CPET) data (where available as part of routine care), and baseline blood test results. Details of the surgical procedure and the delivered anaesthetic (including total intravenous anaesthesia doses if applicable) will also be captured on case report forms at the time of the operation.

#### Biological sample collection

Venous blood samples will be drawn from a newly inserted peripheral venous cannula into tubes for plasma (BD Vacutainer® K2E (EDTA) 10.0mL) and serum (BD Vacutainer® SST™ II Advance 8.5mL) prior to administration of anaesthetic or pre-medication agents. Samples will be centrifuged at 2000G for 10 minutes at 20°C, before dividing plasma and serum into 500µL aliquots and storing at -80°C for later analysis.

At the time of pre-operative spinal anaesthetic, up to 5mL of CSF will be collected into a sterile universal polypropylene container. It will be centrifuged at the same time as the blood samples to remove any cellular debris, and also stored in 500µL aliquots at -80°C for later analysis.

#### Post-operative assessments

Patients will be assessed for delirium each weekday after surgery until hospital discharge using the Memorial Delirium Assessment Scale (MDAS), Observational Scale of Level of Arousal (OSLA), and Hierarchical Assessment of Balance and Mobility (HABAM).

Collateral history regarding cognition, mobility and sleep will be taken from a personal and/or healthcare professional informant.

Routinely collected physiological parameters (temperature, blood pressure, oxygen saturation, heart rate, respiratory rate) will be recorded, as will blood test results and any medication changes.

Post-operative morbidity will be recorded using the Post-Operative Morbidity Survey (POMS), a validated tool for quantifying post-surgical morbidity in 9 domains. This survey will be completed on post-operative days 1, 3, 5, 7, 10, 14 and subsequently every 7 days until hospital discharge. Post-surgical complications will be recorded and graded according to the Clavien-Dindo classification.

### Long-term follow-up

Following discharge from hospital, patients will be contacted by phone for repeat neurocognitive and functional assessment at regular intervals until two years after the procedure. These assessments will be the same as the pre-operative baseline questionnaire, including the TICS-m primary outcome measure.

### Sample analysis

Samples will be analysed using established immunohistochemical methods for detection and quantification of biomarkers. Biomarkers will include, but are not limited to:

- Alzheimer-related biomarkers: amyloid  $\beta$ 1-40, amyloid  $\beta$ 1-42, phosphorylated tau (P-tau)
- Neuroaxonal injury/neurodegeneration: total tau (T-tau), neurofilament light chain (NFL)
- Astrocytic and/or microglial activation: TREM2, MCP-1, S100B, YKL-40
- Inflammation: IL-1, IL-1ra, IL-6, IL-8, TNF- $\alpha$ , IL-2, IL-12, VEGF
- Tissue remodelling: matrix metalloproteinases, brevican
- Neuroprotection: soluble forms of alpha and beta cleaved amyloid precursor protein

### Data analysis

#### *Primary outcomes*

- Absolute change in TICS-m score at 12 months
- Rate of change of TICS-m score up to 12 months

#### *Secondary outcomes*

- Absolute change in ADL score at 12 months
- Rate of change of ADL score at 12 months
- Incidence and severity of postoperative morbidity by POMS
- Incidence and severity of postoperative complications by Clavien-Dindo

#### *Exposures*

- Biomarkers
- Severity and duration of delirium

- Baseline TICS-m score
- Age
- Sex
- Presence of vascular risk factors
- Level of education
- Anaesthetic factors: blood pressure (diastolic BP <60; SBP <80; MAP <75, <69; MAP drop 20% and 30% from baseline; time under curve); hypotension predictive index; BIS; end-organ oximetry including cerebral oximetry; cardiac output.

Outcomes will be analysed using random-effects linear regression with TICS-m score measured two-monthly, adjusted for the exposures above. Between biomarker interactions will be estimated. Bonferroni correction will be performed to account for repeat biomarker testing. Stata 15.0 (StataCorp, Texas) will be used for all analyses.

### Sample size calculation

The present literature on the CSF distribution of biomarkers in delirium is insufficient to provide clear estimates for power calculations. Therefore, we will estimate power for the whole study based on data from the QUB data. The optimal analysis would involve random effects ANOVA, where different distributions of biomarker profiles (factor 1) could be compared with delirium status (factor 2), where the random effects account for the inter-dependence of the biomarker levels. In the meantime, a conservative approach to sample size estimation would be to consider each category of biomarker as a binary parameter (present / absent). In this case, assuming  $\alpha=0.05$  with 4 degrees of freedom (e.g. inflammatory cytokines) and a 20% difference defining biomarker positivity, 298 individuals are needed to detect differences according to delirium status if  $\beta=0.8$  or 395 individuals if  $\beta=0.9$ . A full statistical analysis plan will be published before the study is completed.

Though clinically relevant thresholds are not yet established for dementia, we are likely to be powered to detect even smaller effects given  $n=200$  from PRIMED-risk with  $n=282$  from QUB. Together, these representing the largest repository of perioperative delirium-CSF samples to date with unrivalled opportunities to assay a comprehensive biomarker battery with the power to detect subgroup effects (with/without dementia).

### Regulatory approvals

PRIMED Risk has received ethical approval from Health Research Authority (England) and Health and Care Research Wales / Ymchwil Iechyd a Gofal Cymru, and a favourable opinion from London - South East Research Ethics Committee (Ref. 18/LO/2073; IRAS 234979). Recruitment for all participants will comply with Good Medical Practice and the Mental Capacity Act (2005). A consultee will be approached to consider individuals lacking capacity to decide to participate (elective or emergency patients). This may include the GP or consultant acting as a professional consultee in line with Section 32 of the Mental Capacity Act.

## Dissemination of study results

On study completion, data will be accessible through the Dementias Platform UK repository. Study outputs will be disseminated through journal publications and conference presentations.

## Study status

Study is currently open, with the first 20 (10%) participants recruited.

## Discussion

The PRIMED Risk study represents an opportunity to understand the interacting effects of pre-morbid cognition, surgical and anaesthetic factors, and incident delirium on cognitive outcomes. It will also explore mechanisms underlying these relationships by assessing associated biomarkers of acute and chronic neuronal injury.

PRIMED Risk is related to the broader longitudinal Delirium and Population Health Informatics Cohort (DELPHIC)<sup>16</sup>. DELPHIC investigates the long-term impact of delirium by assessing cognition before, during and after hospitalisation in a whole population setting (urban sample in London, rural sample

in Hereford). With identical clinical assessments, PRIMED Risk has the advantage of sampling from a wider geographical area while focusing on perioperative events and with more detailed biomarker evaluation than DELPHIC. Other ongoing studies with comparable methodological approaches include the SAGES and ASCRIBED cohorts<sup>17,18</sup>.

PRIMED Risk, together with existing data from QUB, sets out to address central questions on perioperative brain health. These concerns are of interest to a range of patient, hospital and public policy stakeholders. We anticipate our findings to contribute to local and national quality improvement work. Given the unmet need around delirium and older surgical patients, PRIMED Risk will systematically describe these and act as a driver for future service development. At the same time, we envisage novel contributions to the understanding of delirium and mechanisms underlying the range of cognitive impairments (including perioperative neurocognitive disorder) associated with surgical procedures<sup>19</sup>.

## Data availability

No data are associated with this article

## References

- Davis DHJ, Skelly DT, Murray C, et al.: **Worsening cognitive impairment and neurodegenerative pathology progressively increase risk for delirium.** *Am J Geriatr Psychiatry.* 2015; **23**(4): 403–15.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Siddiqi N, House AO, Holmes JD: **Occurrence and outcome of delirium in medical in-patients: a systematic literature review.** *Age Ageing.* 2006; **35**(4): 350–64.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Casey CP, Lindroth H, Mohanty R, et al.: **Postoperative delirium is associated with increased plasma neurofilament light.** *Brain.* 2019; **143**(1): 47–54.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hamilton GM, Wheeler K, Di Michele J, et al.: **A Systematic Review and Meta-analysis Examining the Impact of Incident Postoperative Delirium on Mortality.** *Anesthesiology.* 2017; **127**(1): 78–88.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sprung J, Roberts R, Weingarten T, et al.: **Postoperative delirium in elderly patients is associated with subsequent cognitive impairment.** *Br J Anaesth.* 2017; **119**(2): 316–23.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rudolph JL, Marcantonio ER: **Review articles: postoperative delirium: acute change with long-term implications.** *Anesth Analg.* 2011; **112**(5): 1202–11.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Witlox J, Eurelings LS, de Jonghe JF, et al.: **Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis.** *JAMA.* 2010; **304**(4): 443–51.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Davis DH, Muniz Terrera G, Keage H, et al.: **Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study.** *Brain.* 2012; **135**(Pt 9): 2809–16.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Skelly D, Griffin EW, Murray C, et al.: **Acute transient cognitive dysfunction and acute brain injury induced by systemic inflammation occur by dissociable IL-1-dependent mechanisms.** *bioRxiv.* 2017.  
[Publisher Full Text](#)
- Hall RJ, Watne LO, Cunningham E, et al.: **CSF biomarkers in delirium: a systematic review.** *Int J Geriatr Psychiatry.* 2017; **33**(11): 1479–1500.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Sessler DI, Sigl JC, Kelley SD, et al.: **Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia.** *Anesthesiology.* 2012; **116**(6): 1195–203.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cunningham EL, McGuinness B, McAuley DF, et al.: **CSF Beta-amyloid 1-42 Concentration Predicts Delirium Following Elective Arthroplasty Surgery in an Observational Cohort Study.** *Ann Surg.* 2019; **269**(6): 1200–1205.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Buckwalter JG, Crooks VC, Petitti DB: **A preliminary psychometric analysis of a computer-assisted administration of the Telephone Interview of Cognitive Status-modified.** *J Clin Exp Neuropsychol.* 2002; **24**(2): 168–75.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cook SE, Marsiske M, McCoy KJ: **The use of the Modified Telephone Interview for Cognitive Status (TICS-M) in the detection of amnesic mild cognitive impairment.** *J Geriatr Psychiatry Neurol.* 2009; **22**(2): 103–9.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Jackson TA, MacLulich AM, Gladman JR, et al.: **Diagnostic test accuracy of informant-based tools to diagnose dementia in older hospital patients with delirium: a prospective cohort study.** *Age Ageing.* 2016; **45**(4): 505–11.  
[PubMed Abstract](#) | [Publisher Full Text](#)
- Davis D, Richardson S, Hornby J, et al.: **The delirium and population health informatics cohort study protocol: ascertaining the determinants and outcomes from delirium in a whole population.** *BMC Geriatr.* 2018; **18**(1): 45.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Devore EE, Fong TG, Marcantonio ER, et al.: **Prediction of Long-term Cognitive Decline Following Postoperative Delirium in Older Adults.** *J Gerontol A Biol Sci Med Sci.* 2017; **72**(12): 1697–702.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Leavey N, Hammond SP, Shepstone L, et al.: **Study protocol: ASCRIBED: the impact of Acute Systemic Inflammation upon cerebrospinal fluid and blood Biomarkers of brain inflammation and injury in dementia: a study in acute hip fracture patients.** *BMC Neurol.* 2019; **19**(1): 223.  
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Evered L, Silbert B, Knopman DS, et al.: **Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018.** *Br J Anaesth.* 2018; **121**(5): 1005–12.  
[PubMed Abstract](#) | [Publisher Full Text](#)