Inflammation, intrinsic vulnerabilities and postoperative delirium in older people

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Information boxes

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List of abbreviations

AD – Alzheimer's disease

AMT – Abbreviated mental test

CAM – Confusion assessment method

CFS – Clinical frailty scale

CI – Confidence interval

cpRNFL – Circumpapillary retinal nerve fibre layer

CRP – C-reactive protein

DAMPS – Damage-associated molecular patterns

DMN – Default mode network

DSM – Diagnostic and statistical manual of mental disorders

EEG – Electroencephalography

ELISA – Enzyme linked immunosorbent assay

GCIP – Ganglion cell inner plexiform

Gp130 – Glycoprotein 130

HAROLD – Hemispheric asymmetry reduction of older adults

Hz – Hertz

ICU – Intensive care unit

IGF – Insulin-like growth factor

IGFBP – Insulin-like growth factor binding protein

IL – Interleukin

IQR – Interquartile range

MCI – Mild cognitive impairment

MDAS – Memorial delirium assessment scale

MMSE – Mini mental state examination

MRI – Magnetic resonance imaging

NHS HRA REC – National Health Service Health research authority research ethics committee

OCT – Optical coherence tomography

PDR – Posterior dominant rhythm

pEEG – Processed electroencephalography

POD – Postoperative delirium

PRR – Pattern recognition receptors

QUADAS - Quality Assessment of Diagnostic Accuracy Studies

QUIPS – Quality in prognostic studies

RoB – Risk of bias

SD – Standard deviation

SE – Standard error

SMD – Standardised mean difference

TNF – Tumour necrosis factor

Publications, presentations and grants related to this work

Publications

Preoperative inflammatory mediators and postoperative delirium: systematic review and meta-analysis. Noah AM, Almghairbi D, Evley R, Moppett IK. British Journal of Anaesthesia. 2021 Jul 1.

Optical coherence tomography in mild cognitive impairment–Systematic review and meta-analysis. Noah AM, Almghairbi D, Moppett IK. Clinical neurology and neurosurgery. 2020 Sep 1;196:106036

Presentations

Can processed EEG help the anaesthetist predict or reduce postoperative delirium – The John Sear lecture, Society of intravenous anaesthesia (SIVA), November 2023.

Postoperative delirium and the aging brain: Academic Unit 3 academic meeting, University of Nottingham, April 2022

Biomarkers of delirium Sue Watson presentation: Medical School, University of Nottingham, December 2021

Neurological sequelae of COVID-19 associated delirium: Cognitive function, long-COVID, neuroimaging, retinal imaging and biomarkers. PPI meeting February 2021

Postoperative delirium in people age greater than 64 years: PPI meeting, December 2019

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Abstract

Postoperative delirium (POD), an acute and fluctuating confusional state, has the highest incidence (up to 50%) in older (i.e. age ≥ 65 years) people recovering from moderate/major surgery. This is significant in light of the life altering sequelae of POD, e.g. subsequent cognitive impairment, new long-term institutionalisation and increased mortality. While a large body of work has gone into understanding the aetiology of POD, there remains a lot of uncertainty.

Currently, recognised risk factors for developing POD include old age, cognitive impairment, dementia, functional impairment, hearing and/or visual difficulties, comorbidities and severity of illness. There is also a plethora of hypotheses regarding the aetiology of POD. While the neuroinflammatory hypothesis appears to have gained a large following, oxidative stress hypothesis, neurotransmitter hypothesis and neuronal aging hypothesis also have their merits.

These theories point to intrinsic vulnerabilities in different areas. In this work, the argument is made for POD being a symptom of the summation of intrinsic vulnerabilities in diverse areas. However, the individual contributions of each domain need to be measurable, preferably readily and at a reasonable cost.

The aim of this work was to identify and test reliable and readily measurable biomarkers of inflammatory response to surgery and intrinsic brain vulnerability in the context of POD in cognitively intact older people. Concerning intrinsic brain vulnerability, we made the case for preclinical neurodegeneration as a potential cause.

On inflammatory response, our systematic review identified an association between preoperative interleukin 6 (IL-6) and postoperative delirium. Our observational study went further by identifying IL-6 as a fair predictor of POD with an area under the curve (AUC) of 0.753. However, the change in cytokines across surgery was not predictive of POD, nor was the preoperative insulin-like growth factor 3 (IGF-3). Exploration of interactions between key inflammatory mediators and relevant cytokines, soluble receptor or binding protein was also not predictive of POD.

Concerning intrinsic brain vulnerability, a search through the literature on dementia identified two associated features that may be readily measured, i.e. retinal nerve fibre layer (RNFL) thickness measured using optical coherence tomography and resting state posterior dominant rhythm (PDR) on electroencephalography (EEG). RNFL is thinner in people with dementia compared with healthy controls and PDR has lower power in people with cognitive impairment. The systematic review in this work suggests that thinning of the RNFL is associated with mild cognitive impairment (MCI), particularly amnestic mild cognitive impairment. Given our premise of preclinical neurodegeneration contributing to the risk of POD, two studies were conducted exploring RNFL thickness and PDR in cognitively intact older surgical patients. Our study on optical coherence tomography in older hip fracture patients suggests that the RNFL is thinner in people who develop POD compared to those who do not develop POD. Our study on resting state posterior EEG power demonstrated feasibility of acquiring raw EEG data using a processed EEG monitor.

However, there was no significant difference in posterior dominant rhythm between people who had POD and people who did not experience POD.

Identification of measurable and accessible biomarkers of the individual vulnerabilities is critical to unravelling POD in older people.

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Introduction chapter

This thesis will explore potential bedside surrogates of intrinsic brain vulnerability and cytokine dynamics as risk biomarkers for postoperative delirium in older people, i.e. people age ≥ 65 years.

Postoperative delirium (POD), an acute and fluctuating state of confusion, occurs most frequently in older people and has eluded unravelling of its pathophysiology despite efforts by multiple researchers from across the world. While a substantial volume of work has focused on factors associated with ongoing POD, i.e. disease markers, some have investigated risk factors. Whatever the context of biomarker (risk factor or disease marker), there is a preponderance of studies on isolated factors such as preoperative cytokines[1-3], neuroimaging studies[4], processed electroencephalography (pEEG) [5-7] and some pharmacological interventions[8, 9]. Despite this and given our awareness of delirium for over 2500 years, and POD for at least 400 years, progress in understanding POD and ability to devise solutions have been unsatisfactory. By factoring in recent advances in technology, improved understanding of inflammation and neurodegeneration, this work aims to delve deeper into the role of intrinsic brain vulnerability, baseline inflammatory status and inflammatory response to surgery in the aetiology of POD in overtly cognitively intact older people.

Overview of postoperative delirium

Postoperative delirium (POD), a subtype of delirium, is confusion that starts within the first seven days of surgery. Although patients of any age group may experience POD, the incidence is remarkably higher in older people (age ≥ 65 years old). Significantly, POD in older people is associated with adverse postoperative outcomes, i.e. longer hospital stay, increased mortality, higher rate of new admission to long-term institutional care, increased incidence of subsequent new diagnosis of dementia, and worsening of concurrent dementia[10-13]. To state this simply, POD in the older patient is a medical emergency. Currently, there is no pharmacological prophylaxis or cure for POD. That said, non-pharmacological interventions might reduce the incidence/duration of delirium in hospitalised older people[14]. However, global application of these risk reduction strategies is prohibitively expensive. Identification of higher risk patients, and targeting these interventions to this subgroup, may limit the resource burden of implementing risk reduction strategies. Widely recognised risk factors for POD include dementia, cognitive impairment, previous delirium, functional impairment, older age and severity of illness[15]. Given the significance of POD in older people, more sophisticated risk stratification modalities are required. A better understanding of the pathophysiology driving POD may aid the development of more efficient risk stratification tools.

Given that POD is a subtype of delirium, distinguished by its occurrence after an anaesthetic/surgical intervention, the following brief overview of delirium may prove useful.

Definition of Delirium

According to the current edition of Diagnostic and Statistical Manual of Mental Disorders (DSM 5) delirium is an acute onset, fluctuating disturbance in attention and awareness, with an additional disturbance in cognition, which is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to toxins or is due to multiple aetiologies[16]. The diagnostic criteria are outlined in information box 1.

Criteria for the diagnosis of delirium – DSM 5

A. Disturbance in attention (i.e. reduced ability to direct, focus, sustain and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours or a few days), represents an acute change from baseline attention and awareness and tends to fluctuate in severity during the course of the day.

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability or perception).

D. The disturbances in criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin or due to multiple aetiologies.

Information box 1.1: DSM 5 criteria for the diagnosis of delirium

The International classification of diseases 11th edition (ICD 11) states that delirium is characterised by a disturbance of attention, orientation, and awareness that develops within a short period of time, typically presenting as significant confusion or global neurocognitive impairment, with transient symptoms that may fluctuate depending on the underlying causal condition or aetiology.

For POD, the ‘other medical condition’ and ‘multiple aetiologies’ are fulfilled by the surgery/anaesthesia intervention with the possible contribution from the pathology for which surgery is undertaken, e.g. hip fracture or acute abdomen. The study of POD, in view of the unifying major trigger, i.e. the surgery/anaesthesia intervention, gives us a unique opportunity to study and understand delirium while minimising some confounders. That said, there are other factors associated with the surgery such as hospital admission and

disturbance of usual sleep patterns, (all part of the in-patient experience) that contribute to POD incidence.

A short history of delirium and postoperative delirium

Delirium was first included as a diagnostic entity in the third edition of the Diagnostic and Statistical Manual of mental disorders (DSM III) published in 1990. However, the term 'de lira' was first coined in the 1st century AD by Aulus Cornelius Celsus in the context of acute confusional states that occurred in people with fever, head injury, wound infections and even fear. Prior to Aulus Celsus, acute confusional states of similar aetiology were referred to as phrenitis. An early documented reference to phrenitis was by Hippocrates around 500BC. In that era, phrenitis was an acute onset of behavioural problems, sleep disturbance and cognitive deficits associated with fever (if you will, hyperactive delirium). The sister disorder, lethargus, referred to acute confusion associated with inertia, dulling of the senses and enhanced sleepiness (perhaps hypoactive delirium). It is interesting that even in those 'early' days, it was recognised that a person could switch from one form to the other. Soranus of Ephesus, a Greek physician of the 1st century AD also gave vivid descriptions of delirium. He describes loud laughter, murmuring, crying, wrathful to everyone and audible mumbling to oneself[17]. Further evidence of delirium is chronicled in the work of Procopius, a 6th century Greek historian[18]. In his account of the plague in Constantinople, he described clinical scenarios reminiscent of hyperactive delirium ("those who were seized with delirium suffered from insomnia and were victims of distorted imagination, for they suspected men were coming to them to destroy them, and they would become excited and rush off in flight, crying at the top of their voices"). He also documents symptoms that may reflect hypoactive delirium ("forgot all those who were familiar to them, and seemed to lie, sleeping constantly . . . they would eat without waking").

Regarding postoperative delirium, Ambrose Pare, a 16th century military surgeon suggested that severe bleeding during an operation might be a cause of delirium[19]. George Savage also recognised the association between delirium and surgery in his 1887 case series on insanity caused by anaesthesia[20]. In that case-series however, Savage largely put the blame for delirium on the use of anaesthesia (chloroform) on a background of the patient's personal or family history of being weak minded or having overt insanity. He however conceded that 'shock' might be a contributing factor in the development of POD. Interestingly, and astutely, he proposed that "any cause which will give rise to delirium may set up a more chronic form of mental disorder quite apart from any febrile disturbance".

Challenges to unravelling delirium and postoperative delirium

Diagnostic criteria for delirium

The definition and diagnostic criteria for delirium, and therefore postoperative delirium, has changed over the years. While this may be reassuring, as it reflects on-going efforts to clarify and rationalize the definition of delirium, it complicates comparison of research results

across the years. For example, according to DSM IV, delirium is an acute onset, fluctuating change in **consciousness** characterised by a reduced awareness of the environment and a disturbance in attention[21]. This definition was changed in DSM 5 to emphasise the disturbance in **attention and awareness**, instead of change in consciousness. Researchers have reported that the change in criteria has proven to be more restrictive[22, 23]. Meagher et al's study on 768 patients diagnosed delirium in 510 patients using DSM IV criteria, 466 patients using 'relaxed' DSM 5 criteria and 156 patients using 'strict' DSM 5 criteria. They defined strict criteria as requiring all criteria in their most explicit forms and relaxed criteria included features in all possible forms. They demonstrated that the older DSM IV criteria captured people with subsyndromal delirium (by DSM 5 standards), contributing to the discrepancy. Subsyndromal delirium refers to the occurrence of some impairment of cognition in the absence of all the criteria required to diagnose delirium. That said the restrictive effect associated with changes in the diagnostic criteria of delirium is not new. The DSM III revised criteria were also more restrictive than the preceding DSM III criteria[24]. In Liptzin et al's review, 125 people were identified as having delirium using DSM III while DSM IIIR identified 106 people as having delirium in the same cohort.

The current diagnostic criteria for delirium are the DSM 5 criteria (Information Box 1).

Incidence of postoperative delirium

A further challenge to unravelling POD lies in the broad range of reported incidence of POD in older people after moderate and major surgery. According to DSM V POD occurs in 15 – 53% of older individuals. A delve into specialty-specific incidence of POD also replicates this pattern; cardiac surgery (11 – 46%), non-cardiac surgery (13 – 50%) and orthopaedics (12 – 51%)[15]. A focus on an oft performed operation in older people, i.e. hip fracture surgery also demonstrates a wide variation in reported incidence of POD (4 – 53%)[25]. Possible explanations for the wide range may include differences in surgical procedures, methods of delirium assessment and study design[26]. It is plausible that unmeasured confounders in the participants of these studies such as intrinsic vulnerabilities may contribute to the wide range of incidences of POD across different populations. Furthermore, the stated range is from research projects which, in most projects, entails the formal assessment of POD at regular intervals. Unfortunately, in usual care, despite awareness of the significance of delirium amongst healthcare practitioners, implementation of routine screening of hospitalised older people remains suboptimal[27]. The true incidence of POD is therefore unknown. We eager await the report from the United Kingdom's latest sprint national anaesthesia project (SNAP 3) which included postoperative delirium in its objectives.

The changing diagnostic criteria of delirium and POD, and the wide variety in the reported incidence of POD may raise the question 'Is POD a real thing?'

Postoperative delirium – is it a real thing?

Postoperative delirium is a collection of clinical features observed with sufficient frequency and consistency to constitute an 'entity'. This entity does not (? yet) fulfil the definition of a disease, if we accept a disease as having a pathophysiological or pathoanatomical explanation[28, 29]. Could POD be a syndrome? Again, strictly speaking, while POD is a collection of symptoms and signs, it is not associated with a specific disease, at least not as far as we know[30]. Having said that, the constellation of symptoms that constitute hyperactive or hypoactive POD occur with such frequency, that it cannot be ignored. If it is a group of symptoms and signs, the question that naturally arises is 'what is POD a symptom of?'

Before we can answer this question, we must address the role of dyshomeostasis. Given the diagnostic criteria, for delirium to occur there needs to be an externally driven perturbation of the system, surgery in the case of POD. In other words, an internally balanced physiological system does not develop POD or delirium. The dyshomeostasis that results in POD is due to multiple factors including surgery/anaesthesia intervention, cytokine surge, electrolyte imbalance, sepsis, hypoxaemia, environmental factors, absence of hearing and/or visual aids and disruption of the individuals usual sleep-wake pattern[31, 32]. However, not everyone with these challenges to homeostasis develops POD. There, therefore, must be individual intrinsic vulnerabilities that modulate the response to these challenges. By intrinsic vulnerabilities, we allude to brain vulnerability, baseline inflammation status, inflammatory response to surgery, ability to accommodate the inflammatory response to injury and physiologic reserve. This can be conceptualised using the pseudo-equation below and the path diagram depicted in Figure 1.1.

Risk of POD = β_0 + (β_1 x baseline inflammatory mediator dynamics) + (β_2 x inflammatory mediator dynamics across surgery) + (β_3 x intrinsic brain vulnerability) + (β_4 x Environmental factors) + Ɛ

Where β is the individual vulnerability's strength of association with POD and Ɛ incorporates the error and unknowns i.e. lack of understanding/articulation of other factors.

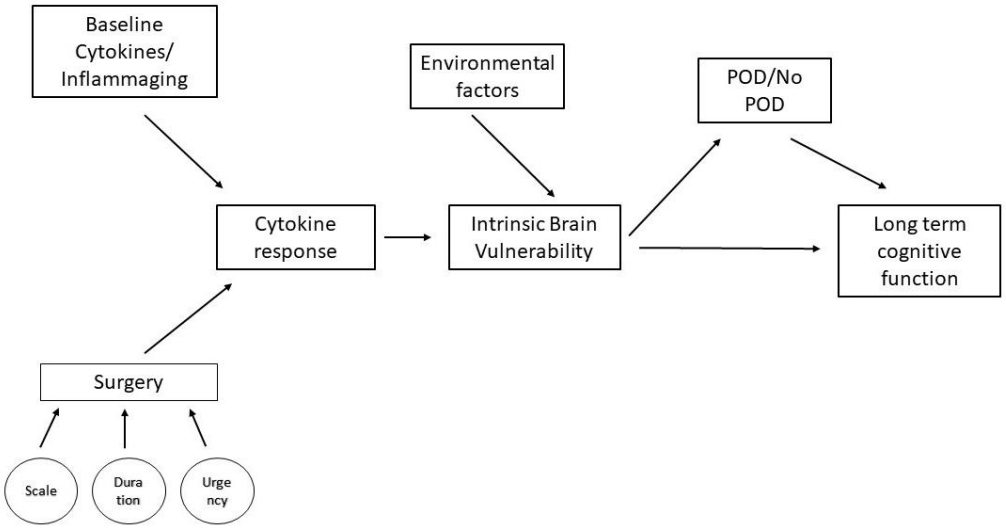

Figure 1.1: Path diagram demonstrating potential association between intrinsic vulnerabilities, POD and subsequent cognitive impairment.

Thus, to answer the question of what postoperative delirium and delirium are symptoms of, it is conceivable that POD may be a symptom of intrinsic vulnerabilities as described above. If confirmed, then POD is a portender of potential future neurological and functional deterioration.

Intrinsic vulnerability - Inflammation

Neuroinflammation and postoperative delirium

Although the precise pathophysiology of postoperative delirium remains unclear, the neuroinflammatory hypothesis is widely accepted as a contributory factor. Neuroinflammation refers to inflammation within the brain (and/or spinal cord). Although a simple definition, neuroinflammation is a complex process that may be protective or harmful. The neuroinflammatory hypothesis suggests that systemic inflammation, via various mechanisms, induces neuroinflammation which may present as delirium[33]. In this section, we will discuss inflammation relevant to aging, provide an overview of the journey from surgery to neuroinflammation and review some relevant actors.

Aging and inflammation

Aging is associated with varying degrees of impairment of the immune response, innate and adaptive[34]. Immunosenesence, a decline in the ability to mount an appropriate immune response to triggers, results in an increased susceptibility to infections[35]. Inflammaging is an

adaptive response, the hallmark of which is an increase in baseline levels of systemic inflammatory mediators such as cytokines[36, 37]. The rate of immunosenescence and inflammaging varies amongst individuals[38].

Specific to the brain, there is evidence of a change in baseline intracranial inflammatory state from anti-inflammatory towards a pro-inflammatory environment with increasing age[39]. In addition, intracranial macrophages (microglia), involved in the local immune response, appear to transition from a resting state to an activated/primed state in the absence of an overt stimulus in the aging brain[40]. This priming is associated with an excessive inflammatory response to subsequent stimuli. Again, these age-related changes in baseline inflammatory status occur at different rates in different people.

Surgery and inflammation

Surgery, which involves deliberate trauma, induces an immune response driven by pro-inflammatory and anti-inflammatory mediators[41]. The pro-inflammatory mediators direct responding agents to the site of injury to promote healing while the anti-inflammatory component aims to localise and attenuate an excessive pro-inflammatory response. The balance between these two processes aims to facilitate tissue healing without adverse systemic effects of inflammation. Damage-associated molecular patterns (DAMPs) released from cells injured by surgery, bind to pattern recognition receptors (PRRs) expressed by immune cells. DAMPs are also called Alarmins due to their role in sending out the alarm that injury has occurred. The resulting molecule (DAMP and PRR) activates, via complex mechanisms, the immune response to injury, a hallmark of which is the production of pro-inflammatory and anti-inflammatory cytokines.

Several authors have demonstrated a rise in various cytokines after surgery, Interleukin 6 (IL-6) being the most often cited cytokine[42-44]. The magnitude of surgical trauma or duration of surgery may influence the extent of the cytokine response[45]. A comparison of the rise in cytokines after hernia repair and elective aortic surgery demonstrated a higher rise in Interleukin 1 (IL-1) and IL-6 after the latter procedure[42]. A systematic review demonstrated an association between the extent of cytokine rise and scale of surgery and further demonstrated a lower cytokine rise after laparoscopic surgery compared to open surgery for the same pathology e.g. cholecystectomy[46]. High postoperative cytokine levels were associated with increased risk of postoperative complications[42, 47].

Cytokines and inflammation

Cytokines, produced by a wide range of cells including circulating immune cells, are endogenous signalling proteins. They are important mediators of the immune system that initiate, perpetuate and down-regulate the immune response. To exert an effect, cytokines bind to the relevant membrane receptor resulting in intracellular transduction of the signal. Although traditionally classified as pro-inflammatory or anti-inflammatory, some cytokines are now understood to be pleiotropic, i.e. have both pro and anti-inflammatory activity, e.g.

Interleukin 6 (IL-6)[48, 49]. There is also a multitude of interactions between different cytokines. For example, IL-6 may inhibit the activity of tumour necrosis factor alpha (TNF-α)[50]. This is mediated by IL-6 driven production of soluble TNF-α receptors. These soluble receptors competitively bind TNF-α in the circulation rendering the TNF-α unavailable for interaction with membrane bound TNF-α receptors. Finally, binding of cytokines in the circulation by other proteins may attenuate or potentiate the cytokine activity. For example, soluble glycoprotein 130 (gp130) inhibits some effects of IL-6[51].

Cytokine production, in response to injury or infection, is a homeostatic process that aims to contain/resolve the trigger and restore pre-injury/infection status, i.e. it is a protective process. However, when there is dysregulation of cytokine response, pathological consequences ensue[52].

Cytokines and neuroprotective agents of interest in this work will now be individually reviewed, however this is a highly simplified description as, in vivo, there are multiple and complex interactions between various cytokines. This is an evolving science.

Interleukin 6 (IL-6)

In the context of inflammation, IL-6 is a pleotropic cytokine that exerts its diverse effects by binding with IL-6 receptor (IL-6R). The IL-6/IL-6R complex then induces dimerization of a transmembrane signal transducer, gp130, resulting in activation of the Janus kinases (JAKs) and, further down, signal transducer and activator of transcription proteins (STATs). STAT (particularly STAT-3) dimers eventually translocate into the nucleus where they modulate the relevant gene's transcription. An alternate pathway involves activation of the mitogen-activated protein kinase (MAPK) pathway by gp130 –JAKs interaction, which ultimately results in modulation of gene expression, cell proliferation or apoptosis. IL-6R may be membrane bound (mbIL-6R) or soluble (sIL-6R). MbIL-6R is present in a limited number of cell types, e.g. hepatocytes and macrophages. SIL-6R, produced by the liver and haemopoietic cells, is abundantly available and aids binding of IL-6 to any cell that has gp130. The type of IL-6R in the IL-6/IL-6R complex influences the effect of gp130 activation. In the classic signalling pathway, IL-6 binds mbIL-6R resulting in anti-inflammatory activity. The trans-signalling, pro-inflammatory pathway is mediated via IL-6/sIL-6R complex[48, 53]. In addition, animal studies suggest that IL-6 requires sIL-6R to induce a neuronal response[54, 55]. As a testament to the complexity of action of cytokines, in the presence of soluble gp130 (i.e. detached from the membrane), sIL-6R may act as an inhibitor of IL-6.

In the brain, IL-6 is produced by microglia, astrocytes and neurons, and has a crucial role in neuronal response to injury. Neuroinflammation is the brain's response to injury which entails activation of astrocytes and microglia and involves the secretion of cytokines and other molecules. Under physiologic conditions, neuroinflammation is a neuroprotective mechanism that aims to contain the insult and facilitate repair. Dysregulated or excessive neuroinflammation results in pathology. Brain-derived IL-6 is pivotal in the neuroinflammatory process as it mediates astrocytosis, microgliosis and preservation of the blood-brain-barrier. In addition, IL-6 aids proliferation and survival of neurons at physiologic

concentrations, however at high concentrations, IL-6 may be associated with neuronal death[56]. Regarding cognitive function, animal studies suggest that high IL-6 has a detrimental effect on learning and memory[53]. As previously stated, availability of sIL6R is important for the function of brain-derived IL-6.

The interaction of systemic IL-6 with the brain is discussed in the 'From systemic inflammation to neuroinflammation' section.

Tumour necrosis factor alpha (TNF-α)

TNF-α, like IL-6, is pleiotropic, i.e. has pro-inflammatory and anti-inflammatory properties[57]. TNF-α may be membrane bound (mTNF-α) or soluble (sTNF-α). The pleiotropy of TNF-α is partly afforded by the variety of TNF receptors available for binding. Binding of TNF-α to TNF Receptor 1 (TNFR1) on the cell membrane mediates pro-inflammatory signalling or cell death; while membrane bound TNF receptor 2 (TNFR2) largely promotes anti-inflammatory signalling and cell proliferation. TNF-α, via TNFR2 activity, contributes to surgical wound healing[58]. Soluble TNF-α preferentially binds to TNFR1s while mTNF-α may activate either receptor. Activation of the TNFR1 pathway, by TNF-α, results in trimerization of TNFR1 allowing the death domain of the receptor to bind with the tumour necrosis factor receptor type 1 associated death domain protein (TRADD). Subsequent ubiquitination and complex pathways determine downstream cytokine signalling (via complex I) or cell death (via complex II). Again, the interactions of TNF-α with other cytokines adds to the complexity. For example, soluble TNF receptors, produced for example by IL-6, may act as an antagonist of TNF-α activity.

Specific to the brain TNF-α is produced by microglia and appears to have both neuroprotective and neurotoxic properties[59]. Research thus far suggests that stimulation of TNF receptors on neurons may be neuroprotective whilst stimulating receptors on microglia leads production and secretion of neurotoxic agents. In addition, the responses to TNF-α are region specific and cannot be predicted by a simple algorithm of TNF-α subtype and receptor stimulated. For example, striatal tissue repair is mediated via TNF-α binding to TNFR1, while in hippocampal tissue repair, the receptor appears to be TNFR2[60]. The spectrum of activity of brain-produced TNF-α and receptors in different tissues in the brain is complex and yet to be fully elucidated.

The mechanism by which systemic TNF-α contributes to neuroinflammation is discussed in the 'From systemic inflammation to neuroinflammation' section.

From systemic Inflammation to neuroinflammation

Ideally, an investigation of the role of neuroinflammation in the pathogenesis of POD would involve direct measurement of the brain's inflammatory mediators. However, the practical challenge this poses in vivo has resulted in the use of surrogates such as CSF and, more frequently, blood levels of inflammatory mediators (including cytokines).

As described above, surgery is associated with an increase in systemic cytokines, which peaks approximately two days after surgery and may last over a week[42, 43]. It is important to identify how these systemic cytokines influence the brain, POD being a neuropsychiatric symptom. There is some evidence of an association between systemic cytokines and some aspects of cerebral dysfunction. A study in which endotoxin was administered intravenously demonstrated a rise in blood cytokines and transient increase in depression and impairment of memory[61]. Another study demonstrated an association between serum levels of IL-6 and cognitive decline in older people[62]. Finally, a positron emission tomography study demonstrated an association between change in microglial activity and systemic TNF-α activity after robotic prostatectomy[63].

Current understanding suggests that systemic cytokines transmit information to or enter the brain via a neuronal and a humoral pathway. The neuronal pathway is via afferent neurons from the relevant body part. In abdominal surgery or infection, vagal afferents receptors are stimulated by circulating cytokines e.g. IL-1 (increased due to surgery or infection). The vagal nerve then transmits this signal to areas in the brain including the brainstem, hippocampus and limbic structure[64]. This is likely a major pathway by which systemic infection results in sickness behaviour, i.e. lethargy, anorexia and reduced activity. In the humoral pathway, circulating cytokines act at the blood-brain-barrier (BBB) and via areas of the brain devoid of a BBB. At the BBB, systemic cytokines can induce perivascular macrophages to produce cytokines with resulting stimulation of microglia[65, 66]. In addition, there are cytokine-specific, saturable transporters in the BBB that facilitate a limited amount of cytokine transfer, particularly IL-1, IL-6 and TNF-α, across the BBB[67]. Areas devoid of the BBB such as the circumventricular organs are rich in macrophage-like cells which, when stimulated by systemic cytokines, produce IL-1 resulting in neuroinflammation[66]. Also, because these areas are devoid of a BBB, diffusion of systemic cytokines into the brain parenchyma is unrestricted, facilitating their direct action on microglia. The state of activation of the microglia (resting or primed) is critical to determining the extent of their response to the system-to-brain mechanisms described.

Systemic inflammation and postoperative delirium

Baseline blood levels of cytokine and postoperative delirium

Researchers have explored the association between baseline (i.e. preoperative) blood levels of various cytokines and the incidence of POD with conflicting findings. A study on hip fracture surgery patients found that preoperative IL-6 was higher in people who developed POD compared to those who did not develop POD[68]. However, given the inflammatory response that must already be in play due to the fracturing injury, the preoperative cytokine levels do not reflect the participants' true baseline. That said, in a mixed (acute and elective) hip surgery study, preoperative levels of IL-6, C-reactive protein (CRP) and insulin-like growth factor 1 (IGF-1) were not significantly different between POD and no POD groups[1]. Another report on a mixed cohort of older people undergoing emergency or elective surgery found an association between elevated preoperative blood level of IL-6 and

increased incidence of POD ($p = 0.021$)[2]. Yet another study on older, abdominal surgery patients did not find a difference in the IL-6 levels between people who developed POD compared to those who did not develop POD[69]. Preoperative cytokine levels in a study on cardiac surgery patients were also not significantly different between people who developed POD and those who did not[70].

Given the conflicting results of various studies, the role of preoperative systemic inflammation in the aetiology of postoperative delirium remains uncertain.

Postoperative blood levels of cytokines and postoperative delirium

As discussed, the extent of surgery has an impact on the scale of postoperative cytokine rise especially IL-6, IL-1 and TNF-α. Several researchers have investigated if there is an association between early postoperative cytokine levels and the incidence of postoperative delirium.

Support for the hypothesis that high postoperative cytokine levels may be associated with an increased incidence of postoperative delirium is provided by a study on people undergoing abdominal surgery[69]. Higher cytokine levels (IL-6) at 24 hours and 48 hours after surgery was associated with increased risk of POD. Another study on hip fracture surgery patients also associated a high early postoperative IL-6 with increased incidence of POD[68]. In addition, the highest levels of IL-6 occurred during the POD episode. A study on cardiac surgery patients also showed an association between POD and high IL-6[71]. However, participants in that study do not appear to have had preoperative IL-6 assessments. Inclusion of preoperative IL-6 values may have been more instructive especially regarding the trajectory of IL-6 in these patients. Interestingly, another cardiac surgery study did not find an association between postoperative IL-6 levels and incidence of POD[70]. In a cohort of older people undergoing total hip replacement, there was no association between the pre- or post-operative levels of various cytokines and the incidence of postoperative delirium[72].

Yet again, there are conflicting results that require further investigation. That said there is a preponderance of studies that suggest higher levels of postoperative cytokines may be associated with an increased risk of POD. The question arises as to whether this is solely a reflection of the cytokine surge induced by the surgery/anaesthesia intervention (i.e. absolute value of cytokines) or consequence of the extent of change from the individual's baseline (i.e. relative value).

Insulin-like growth factor 1 and postoperative delirium

In this discussion on cytokines and neuroinflammation, a brief discussion of a key neuroprotective hormone, i.e. insulin-like growth factor 1 (IGF-1) is useful.

IGF-1, an anabolic mediator of growth hormone, has antioxidant and anti-inflammatory properties, and is neurotrophic. IGF-1 promotes postnatal brain growth, aids direction of neuronal regeneration, supports neurogenesis and inhibits apoptosis[73]. Growth hormone

(GH), produced by the pituitary gland, binds to and activates growth hormone receptor (GHR) which is present on the cell membrane of a wide variety of tissues throughout the body. Activated GHR triggers the JAK-STAT pathway, which via increased IGF-1 gene expression leads to IGF-1 secretion. While the liver produces the majority of serum IGF-1, a wide variety of tissues synthesize small amounts of IGF-1, largely for paracrine or autocrine activity. The majority of IGF-1 produced by the liver is transported in plasma bound to IGFbinding proteins (IGFBP), leaving a small amount (~1%) of free IGF-1 immediately available for IGF-1 receptor (IGF-1R) activation[74, 75]. IGF-1 receptors occur in a wide variety of tissues including the brain. Systemic IGF-1 can cross the BBB via transmembrane transporters and activate the intracranial receptors. In addition, there is evidence of locally produced IGF-1 in the brain but the proportionate contribution to intracranial IGF-1 activity is unclear[76]. Activation of IGF-1R results in intracellular transduction of the signal, activation of a variety of signalling pathways resulting in diverse outcomes e.g. Protein kinase B pathway activation for cell proliferation. Unfortunately, stimulation of cell proliferation may partly explain the association between high serum IGF-1 levels and cancer[77, 78]. It is important to note that binding of IGF-1 to IGFBP in the blood stream, while providing a reservoir of IGF-1, may also act as an antagonist of IGF-1 activity. Although there are six IGFBPs described that can form complexes with IGF-1, the main binding protein is IGFBP-3. Complicating the picture is that IGFBP-3 also binds other molecules, e.g. IGF-2 and plasminogen, making the relative concentrations of other ligands and prior occupation of binding sites a factor. In the context of older people, aging is associated with reduced serum and brain levels of IGF-1 and a decrease in the BBB transporter of IGF-1[79].

Given the neuroprotective, anti-inflammatory properties of IGF-1, a few researchers have explored the role of serum levels of IGF-1 in the aetiology of POD. A study on older, elective gastrointestinal surgery patients, reported lower preoperative IGF-1 levels in patients who developed POD[80]. However, another study on older patients undergoing knee arthroplasty did not demonstrate a significantly lower preoperative IGF-1 level in people who subsequently developed POD compared to those who did not[81]. Considering the complex interactions of IGF-1 and measurement of IGF-1 in isolation, without consideration of modifiers of IGF-1 such as IGFBP-3, the conflicting findings are not surprising.

Summary of Inflammation

The surgery/anaesthesia intervention is associated with a rise in inflammatory mediators, which may have trophic or adverse effect on brain function, depending on the scale of inflammatory mediator rise. However, from results of current research, the association between systemic inflammatory mediator levels and POD is not consistent. In older people, individual degrees of inflammaging and priming of microglia may modify the severity of neuroinflammation triggered by systemic cytokines thus influencing the propensity for POD. In addition, the influence of interactions between cytokines and other mediators must be considered. Finally, age-related reduction in the availability of the anti-inflammatory hormone IGF-1 and the extent of binding by IGFBP-3 may be a contributory factor.

Intrinsic vulnerability – Brain vulnerability

With regards to the suggested hypothesis that intrinsic brain vulnerability may be a contributory factor to the development of POD in overtly cognitively intact older people, the frame of reference of this work is on the trajectory of neurodegeneration, i.e. 'cognitively intact, no neurodegeneration' to 'overtly cognitively intact with covert neurodegeneration' to 'mild cognitive impairment' then 'overt neurodegenerative disease'. While other established neurologic pathologies may have an association with increased risk of POD, neurodegenerative disease is especially important because of the occurrence of a covert prodromal period, often of significant duration[82, 83]. Following is a brief discussion of brain aging, established neurodegeneration and other non-neurodegenerative studies relevant to POD.

Aging and the brain

Disentangling/discriminating between physiologic brain aging and preclinical pathological neurodegenerative changes, at a group or single subject level, is challenging. Neurodegenerative changes may predate the clinical features of Alzheimer's disease by up to a decade. That said there are some widely accepted structural and functional features of physiologic brain aging. These include reduced brain volume, increased white matter hyperintensities, dysregulated energy metabolism, aberrant neural network activity and neurotransmitter depletion[84, 85]. The impact of aging on inflammation was reviewed in the intrinsic vulnerability – inflammation section.

While the pathogenesis of aging is not fully elucidated, there are several hypotheses, broadly divided into programmed theory and damage/error theory[86]. Thrown into the mix and specific to neural function are theories of compensation for aging deterioration such as the scaffolding theory of aging and cognition (STAC)[87]. STAC suggests that in response to the attrition of aging, the brain develops new networks to ameliorate the adverse effects of functional decline, i.e. neuroplasticity, an example of which may be hemispheric asymmetry reduction in older adults (HAROLD)[88]. The process of brain aging is dynamic.

Neurodegeneration and postoperative delirium

Concurrent dementia or mild cognitive impairment (MCI) is associated with an increased incidence of POD (relative risk 2.8 and 3.5 - 4.2 respectively)[15]. Alzheimer's disease (AD), an exemplar of pathological aging of the brain, is one of the most common causes of dementia. Other examples of neurodegenerative conditions that are associated with dementia are Parkinson's disease, cerebrovascular disease, and Huntington's disease.

These neurodegenerative disorders may increase the incidence of or susceptibility to POD in a few ways. Many neurodegenerative disorders involve some degree of neuroinflammation and the notion that neuroinflammation may induce neurodegeneration is gaining support in

the academic community[89, 90]. There is also some loss of neurological reserve associated with neurodegenerative disorders. It is clear that by the time patients present with clinical features of dementia a significant proportion of neuronal damage has occurred in the preceding years[91, 92].

Given that the neurodegenerative changes that result in overt AD-associated dementia may precede symptoms by up to a decade, a proportion of overtly, cognitively intact older people presenting for surgery may already have covert neurodegeneration. A study on non-demented older people undergoing elective surgery demonstrated an association between preoperative magnetic resonance imaging finding of cortical thinning and the severity of POD[93]. The relevance of this lies in the association between cortical thinning and AD which is demonstrable from the early stages of AD[94]. These early neurodegenerative changes may constitute intrinsic brain vulnerability.

On the topic of neurodegeneration, there is an association between postoperative delirium and a subsequent diagnosis of cognitive decline/ dementia. A longitudinal study on people age ≥ 85 years demonstrated an associated between the incidence of delirium and an increased risk of subsequent dementia (Odds ratio 8.7, 95% confidence interval 2.1 - 35)[12]. Another study on people age ≥ 65 years undergoing hip fracture surgery reported the incidence of new diagnosis of dementia after surgery was 69% in people who experienced POD vs 20% who did not experience POD[95]. In a subgroup analysis of the Mayo clinic study of aging, 1152 people who were overtly cognitively intact at the time of surgery were assessed[96]. The occurrence of POD was associated with increased odds of subsequent dementia or MCI (adjusted odds ratio 3.00, 95% confidence interval 1.12 – 8.05). The question arises as to whether POD causes dementia. It is plausible that POD does not cause dementia but rather it unmasks the already covertly vulnerable brain. In other words, covert neurodegeneration may be a risk factor for POD in **some, not all**, cognitively intact older people who experience POD. That said, there is also some suggestion that delirium in medical patients with dementia may be associated with faster deterioration accelerated worsening of cognitive function[97].

Non-neurodegenerative brain vulnerability and postoperative delirium

With increased access to brain magnetic resonance imaging (MRI), there is an increasing awareness of abnormal features such as white matter hyperintensities (WMH). WMH may be a result of microvascular disease, leakage of plasma into white matter and consequent demyelination[98]. While WMH may be present in normal older brains, increased expression may be associated with an increased incidence of dementia (hazard ratio 1.9, 95%CI 1.3 – 2.8) and cognitive dysfunction[98, 99]. Current literature was therefore searched for evidence of an association between non-neurodegenerative brain MRI findings and POD. First, a brief overview of neuroimaging and cognition in the context of POD.

Neuroimaging and cognition

Cognition

Cognition refers to the processes whereby knowledge is acquired, understood, stored and retrieved. It is the sum of mental activities involved in acquiring and processing information, i.e. the mental processes required for everyday living. DSM-5 describes six neurocognitive domains, i.e. complex attention, executive function, learning and memory, language, perceptual-motor and social cognition. Delirium can present with features in any of these domains[100]. Given the range of cognitive domains, a knowledge of the brain areas mediating specific cognitive domains would aid the interpretation of anomalies on brain imaging, i.e. the neuroanatomy of cognition. Unfortunately, current understanding of the neuroanatomy of cognition is an evolving and complex science. However, some associations between anatomical location and cognitive function have been identified. The caudate nucleus and frontal cholinergic pathways play a role in attention[101], right parietal and right prefrontal areas mediate sustained attention, and extensive network including the cerebellum and anterior cingulate cortex are important for selective attention[102]. In addition, the non-dominant parietal and temporal cortex are implicated in orientation[103, 104] and frontal and temporal lobes in sentence comprehension[105].

Neuroimaging

The foregoing is but a small sample that demonstrates the complexity of the neuroanatomy of cognition. Even if we could pinpoint a well-defined brain area that subserves a specific aspect of cognition, there is a complexity of interwoven relationships between multiple areas as well as hierarchies of relationship, such as higher order association areas, that make static anatomical localisation insufficient for describing the neuroanatomy of cognition. The connectivity, structural or functional, must be considered.

Structural/anatomical connectivity, i.e. physical contact or continuity between neurons usually via white matter fibres, may be imaged using diffusion tensor imaging (DTI). DTI measures random motion of water in tissues (mainly the white matter connections), and variations in the direction or magnitude of random motion of water may indicate structural connectivity anomalies[106].

Functional connectivity refers to areas of the brain that are co-activated during execution of a specific task, a neural network, and may be measured using functional magnetic resonance imaging (fMRI). Anatomical connectivity is not a requirement for functional networks. FMRI may be used to assess task state networks (networks involved in a specific task) or resting state networks (areas that have increased co-activity during a period of no specific activity). The default mode network (DMN) is a resting state network of areas of the brain that have greater activity in the resting state than in external task focussed states. It includes the medial parietal cortex, medial prefrontal cortex, posterior cingulate cortex and medial temporal lobes (which includes the hippocampus and parahippocampus). The DMN is important for self-reference, autobiographic information, theory of mind, moral reasoning, social evaluations and episodic memory.

Delirium may be a manifestation of a breakdown of the above networks[107]. The hypothesis suggests that the extent to which the breakdown occurs on exposure to a precipitant of delirium depends on the pre-exposure baseline connectivity and the level of inhibitory tone. Interestingly, disrupted functional connectivity has been demonstrated in mild cognitive impairment and Alzheimer's disease when compared with age matched controls[108, 109]. If the hypothesis is proven, the question arises as to whether the baseline network disruption is an indicator of covert neurodegeneration.

Preoperative neuroimaging and postoperative delirium

A literature search was conducted to identify studies on POD on preoperative brain MRI and the incidence of POD. The search was conducted in Medline using search terms postoperative delirium and magnetic resonance imaging as keywords and in many places. The keywords were combined using the Boolean operator 'AND'. Structural, structural connectivity and functional MRI studies were included. Studies in which the neuroimaging occurred after surgery, or during an episode of POD, were excluded because the findings may reflect neurological consequences of cytokine dynamics and/or POD.

Structural MRI and POD

A retrospective, case-control, MRI study comparing 23 patients who experienced POD after lung cancer surgery with age- and gender-matched controls demonstrated an association between preoperative white matter abnormality burden and incidence of POD. There was no significant difference in cerebral atrophy between the two groups[110]. In another retrospective study on 130 patients undergoing cardiac surgery, 18 developed POD. The burden of severe white matter hyperintensities was an independent predictor of POD[111]. A prospective study on 98 patients undergoing off-pump cardiac surgery also reported similar results[112]. Preoperative gray matter volume in the context of POD has also been studied. In a prospective study on 116 consecutively recruited cardiac surgery patients with an age range of 58 to 84 years, 19 developed POD. There was significant reduction of gray matter volume in the transverse temporal gyrus, middle temporal gyrus, occipitotemporal gyrus and hippocampus of people who developed POD compared to those who did not[113]. In another study on 57 older hip fracture patients, 25 had POD[114]. The high incidence of POD in this cohort is concerning but may be the result of inclusion of people with dementia and low cognitive scores in the study. That said, reduced gray matter density in the right dorsomedial prefrontal cortex, left paracentral lobule, left middle temporal gyrus, right inferior temporal gyrus, left caudate/suprachiasmatic nucleus, right posterior cingulate cortex, left hippocampus and left cerebellum was demonstrated in participants that subsequently developed POD. However, a study on 146 consecutively recruited, cognitively intact older people undergoing elective surgery, of whom 32 developed POD, did not support these findings[115]. The study did not find a difference in preoperative white matter hyperintensities or gray matter density in people who developed POD compared to those who did not. A systematic review also did not find a statistically significant association

between preoperative brain volumes or white matter hyperintensities and the incidence of postoperative delirium[116]. Overall, the wide variability in the location of pathological changes where identified and conflicting findings regarding the neural substrate of POD suggests more work is required to validate or refute an important association between non-neurodegenerative brain anomalies and the incidence of postoperative delirium.

Structural connectivity and postoperative delirium

There are a few studies that used preoperative structural connectivity, assessed by DTI, to try to identify the neural substrate of POD. A cohort of 136 dementia-free older people undergoing elective surgery, of whom 29 developed postoperative delirium, had preoperative DTI[4]. After adjusting for age, gender, vascular comorbidity status and general cognitive performance there was an association between the incidence and severity of POD, and DTI abnormalities (decreased fractional anisotropy (FA) and/or increased mean, axial and radial diffusivity) in the cerebellum, cingulum, corpus callosum, internal capsule, basal forebrain, thalamus, occipital, parietal and temporal lobes, including the hippocampus. Decreased FA in the right external capsule was also associated with subsequent development of delirium in a study on 57 older patients undergoing hip fracture surgery of whom 25 had POD[114]. Widespread significant reduction in fractional anisotropy on preoperative MRI scan was associated with the incidence of POD after cardiac surgery in a study on 116 patients of whom 19 had POD[117]. Again, while it appears that preoperative anomalies in structural connectivity may be associated with the risk of POD, the wide variety of locations suggests that there is a requirement for more data in this area.

Please see Information box 1.2 for definitions of some structural connectivity terms used[118].

Fractional anisotropy (FA): the degree of anisotropy of a diffusion process i.e. the degree to which water's measured apparent diffusion coefficient varies with tissue orientation. Measured from zero (diffusion is unrestricted or equally restricted in all directions called isotropic diffusion) to one (diffusion occurs only along one axis)

Axial diffusivity: Diffusivity over the principal axis i.e. the longitudinal axis of the anisotropic structure.

Radial diffusivity: Diffusivity over the minor axes i.e. the perpendicular axis of the anisotropic structure.

Mean diffusivity: The overall magnitude of water diffusion independent of anisotropy.

Information box 1.2: Structural connectivity definitions

Functional connectivity and postoperative delirium

The previously discussed study on older hip fracture surgery patients (n = 57 of whom 25 developed POD) also explored preoperative functional connectivity as part of a neural substrates of POD research project[114]. In their resting state MRI study, an increased amplitude of low frequency fluctuation in the right dorsolateral prefrontal cortex was observed in patients who subsequently developed POD compared to those who did not. Conversely, a recent study on 246 older, major surgical patients, of whom 38 developed POD, did not demonstrate a difference in preoperative predefined functional connectivity parameters (global functional connectivity strength, diameter, and leaf fraction) between groups[119]. However, preoperative hyperconnectivity in three preselected networks was associated with subsequent POD in an older, surgical cohort of 283 patients of whom 42 had POD[120]. The networks were based on seeds in the orbitofrontal cortex, nucleus accumbens, and hippocampus. The authors attribute this hyperconnectivity to possible compensation for subtle brain dysfunction.

Please see Information box 1.3 for definitions of some functional connectivity terms used[121].

Amplitude of low-frequency fluctuations: Measured in the resting mode, this is a measure of MRI signal intensity spontaneous fluctuations. These spontaneous fluctuations are a normal occurrence in the resting brain. It is the total power within the frequency range of 0.01 to 0.1 Hz.

Node: Gray matter regions

Diameter: Number of edges connecting the most remote nodes. A lower diameter implies more efficient processing of information between remote regions in the brain.

Leaf nodes: a node with only one connection

Minimum spanning tree (MST): a network containing the strongest connections from the set of all available weighted connections

Leaf fraction: Fraction of leaf nodes in the MST. Higher leaf fraction means the network is largely dependent on central nodes.

Betweenness Centrality: Fraction of all shortest paths that pass through a particular node.

Information box 1.3: Functional MRI terminology definitions

Summary of preoperative imaging and postoperative delirium

Interpreting functional networks in the older age-group is made complex by the potential of adaptive response to aging or neurodegenerative challenges, e.g. STAC as discussed above. It is therefore difficult to draw any conclusions from the limited and conflicting information currently available on neuroimaging for non-neurodegenerative neural substrates of POD. For macrostructural changes, the findings have been inconsistent and, for each finding, there is a limited amount of evidence in support of or against it. The widespread locations of abnormalities found as highlighted above makes identification of key features difficult. For now, it seems that in the absence of gross brain pathology such as neurodegeneration, cerebrovascular accident, traumatic brain injury, there is currently no scientific evidence of well-defined structural connectivity and functional connectivity abnormalities, as determined by magnetic resonance imaging, which play a major role in the aetiology of POD.

Biomarkers

A biomarker is defined by the Biomarkers' Definitions Working Group as "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention"[122]. A biomarker must be reliably associated with the condition it indicates. Measurements must be objective, reproducible, precise and accurate[123]. Different classes of biomarkers include risk, predictive, diagnostic, monitoring, or prognostic. Specific to POD, there have been efforts to identify risk/predictive biomarkers including blood, CSF and neuroimaging[124-126] and a plethora of postoperative delirium or delirium biomarker reviews[127, 128]. Unfortunately, close study of these articles has not highlighted a consistent candidate. This is not surprising given that POD may be a symptom of the amalgamation of vulnerabilities in diverse domains (e.g. brain, inflammation, and environment). In this context, the probability of discovering a single biomarker that is reliably predictive of POD is remote. Rather the collective effect of biomarkers of individual vulnerabilities may prove more pragmatic.

Potential biomarkers of covert neurodegeneration

Thus far, we have suggested that intrinsic brain vulnerability may contribute to the development of POD in overtly cognitive older people. The case has also been made for preclinical neurodegeneration as the most likely form of intrinsic brain vulnerability based on its long preclinical period and the significant incidence of dementia after an episode of POD[129]. Several MRI studies have demonstrated preclinical brain changes associated with subsequent MCI/dementia[82, 130]. However, MRI is prohibitively expensive and logistically difficult to use as a routine tool for screening for covert neurodegeneration. More easily accessible tools are required to screen for biomarkers of intrinsic brain vulnerability. In this section we will discuss biomarkers and tools identified from dementia research that may be used to quantify intrinsic brain vulnerability in the context of POD. These tools are optical

coherence tomography (OCT) used to measure retinal nerve fibre layer (RNFL) thickness in this context and electroencephalography (EEG).

Optical coherence tomography, retinal nerve fibre layer thickness, aging and neurodegeneration

Optical coherence tomography (OCT) is an imaging technique based in interferometry, uses low coherence light to obtain cross sectional imaging of superficial tissues (figure 1.2)[131]. Interferometry is the measurement of the intensity of a split reflected wave. The wave (e.g. monochromatic light) from the source is projected to a half-silvered mirror which splits the wave into two beams. One beam proceeds unrefracted through the half-silvered mirror to a reflecting mirror. The wave reflected from this mirror is refracted by the half-silvered mirror to a detector. The second beam of the original wave is refracted at about 90 degrees by the half-silvered mirror to its own reflecting mirror. This reflected wave passes, unrefracted, through the half-silvered mirror to the detector. The image formed on the detector depends on the phase difference between the two received waves. The phase difference is determined by the relative distance of the reflecting mirrors to the half-silvered mirror. This phase deference determines the interference (constructive or destructive) of the waves at the detector.

In OCT, the light source uses light waves that are partially coherent, i.e. have a small phase difference. Thus, useful interference occurs over a short distance called the coherence length and can be used to obtain high resolution images.

First described by Huang et al in 1991 OCT, now widely available across the world, is used largely in ophthalmology and is gaining a foothold in other clinical areas. Incidentally the original paper on OCT discussed its use in peripapillary retinal imaging (figure 1.3) and the coronary artery.

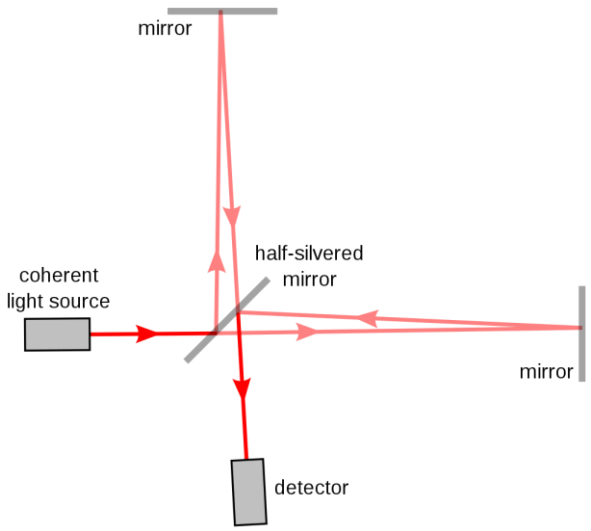

Figure 1.2: Schematic of interferometry, the basis of OCT

Image courtesy of Stannered, CC BY-SA 3.0 <http://creativecommons.org/licenses/by-sa/3.0/>, via Wikimedia Commons

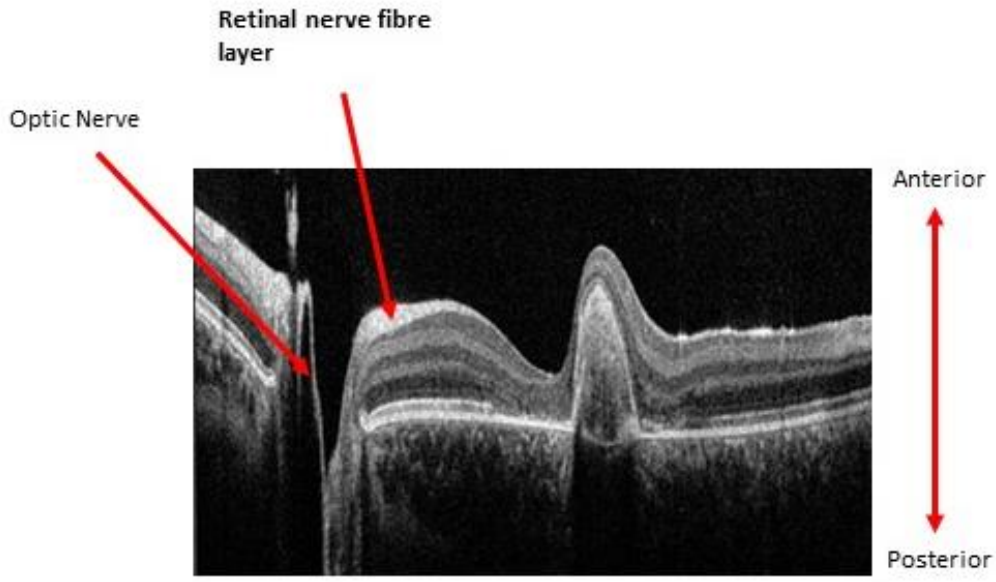

Figure 1.3: Cross sectional image of the retina

The retinal nerve fibre layer (RNFL) is the layer formed from the axons of the ganglion cell layer of the eye. As a result of its high visibility on OCT, affording ease of delineation and measurement, many researchers have investigated the effect of local eye disease and systemic disease on the thickness of the RNFL as measured by OCT[132-134]. However, the RNFL thickness is also affected by physiologic factors such as age, race and refractory error[135-137]. Although stable in the short term, the RNFL gets progressively thinner with age. Unfortunately, the rate of change per year varies with study, ranging from 1.5µm/decade to 0.52µm/year.

More significant is the association of thinning of the RNFL with overt neurodegeneration. A study comparing the RNFL thickness in people with Alzheimer's disease, Lewy body dementia, Parkinson's dementia and age-matched controls found the RNFL was significantly thinner in each type of dementia than in controls[138].

The retinal nerve fibre layer largely consists of myelinated axons of retinal ganglion cells. Thinning of this layer in AD is not surprising considering evidence of brain white matter degeneration in AD[139]. Of note, myelin anomalies may precede pathological amyloid and tau

accumulation in AD[140]. Also, an inverse relationship between macular RNFL volume and neocortical amyloid accumulation has been described[141].

More significantly, longitudinal studies suggest that RNFL thickness is inversely associated with future cognitive deterioration and dementia[142, 143]. The latter suggests that RNFL measured with OCT may be a candidate biomarker for intrinsic brain vulnerability. There were no studies identified on RNFL thickness and postoperative delirium.

Electroencephalography, aging and neurodegeneration

Electroencephalography (EEG) is an indispensable means of assessing brain physiology. While MRI has the advantage of spatial resolution, EEG provides great temporal resolution albeit with lower spatial resolution. EEG measures the relative variations in summated excitatory and inhibitory post-synaptic electric potentials from the neurons underlying the location of the relevant EEG electrode. The columnar arrangement of cortical pyramidal neurons allows summation of the electric potentials thereby enhancing the signal.

The EEG signal is a composite waveform of the different frequency bands (Figure 1.4)

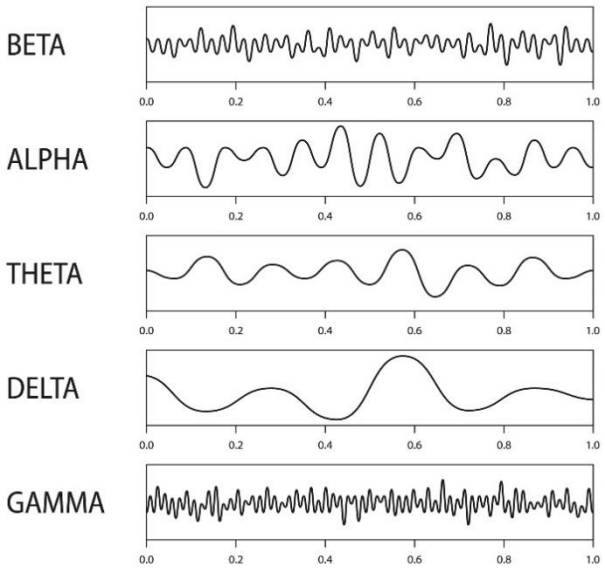

Figure 1.4: The canonical frequency bands of the electroencephalogram

Deciphering EEG changes associated with normal aging also comes with the caveat regarding the blurred transition from healthy aging to pathologic aging. That said, a large body of work suggests that physiologic aging is associated with global slowing of the background waveform, reduced amplitude of alpha and beta rhythm and increase in delta and theta power in resting state EEG[144]. However, while the power reduction in the low

alpha bandwidth has been consistent across a number of studies, the findings regarding the amplitude of delta rhythm with increasing age have been conflicting[145, 146]. In the latter study on 215 cognitively intact participants of age range 18 – 85 years, resting state (eyes closed) EEG demonstrated a progressive reduction in amplitude of the occipital delta rhythm and decreased power in low frequency (8 – 10.5Hz) alpha rhythm over the parietal, occipital and temporal areas with increasing age.

Alzheimer's disease, a very common neurodegenerative condition, is our exemplar for pathological brain aging and mild cognitive impairment is our example of an intermediate category of cognitive impairment. Oft cited effects of Alzheimer's disease on resting state EEG is global slowing resulting in a shift of the power spectrum to delta and theta frequency bands and reduced coherence[147, 148]. However as previously stated, global slowing appears to be a frequent EEG feature of aging. The question arises as to how to distinguish the EEG features of neurodegeneration from those of physiological aging. A multicentre, resting (eyes closed) EEG study sought to address this question. Grouping variable of participants were normal old (126 participants), MCI (155 participants) and mild AD (193 participants)[149]. In that study, the amplitude of low frequency alpha rhythm was normal old > MCI > mild AD in the occipital, parietal, temporal and limbic areas. Occipital delta amplitude was normal old < MCI < Mild AD. Significantly, the study also demonstrated a correlation between low-frequency alpha rhythm and mini mental state examination (MMSE) scores. A later study by the same group also found a reduction of occipital alpha amplitude during resting-state eyes closed EEG with progression from normal old through MCI to AD[150]. The same study demonstrated a similar reduction trend, on MRI, in occipital grey matter density from normal old to AD and a correlation between amplitude of occipital alpha rhythm and occipital grey matter density.

In conclusion, there is the potential that EEG may detect underlying neurodegenerative disease, however, it is important to note that the evidence thus far is based on group level and not individual discrimination.

Processed electroencephalography (pEEG) and postoperative delirium

A discussion of EEG in the context of anaesthetic research would not be complete without touching on processed electroencephalography (pEEG) and POD. PEEG is a non-invasive, single or two channel, brain-monitoring device that is now part of usual anaesthesia care. As currently used, the pEEG device continuously acquires raw, single or two channel EEG, via adhesive cutaneous sensors placed on the patient's forehead. Proprietary algorithms determine a depth of anaesthesia index number based on the raw EEG. The anaesthetist uses this number to guide titration of anaesthesia dose (Figure 1.5).

Figure 1.5: Processed EEG monitor displaying EEG waveform and depth of anaesthesia index

Depth of anaesthesia index number and POD

Several studies have investigated the impact of depth of anaesthesia index on the incidence of POD in older people with mixed results. Early studies demonstrated an association between lower depth of anaesthesia index and increased risk of POD in older people[6, 7, 71]. However, a closer look at the cognitive dysfunction after anaesthesia (CODA) trial, an RCT conducted on 921 older people, which demonstrated a lower incidence of POD in the pEEG-guided group raises some interesting questions[7]. Specifically, the difference in anaesthetic dose between the pEEG guided and the usual care arms; effect site concentration for propofol of 2.7 vs 3.3 respectively and minimum alveolar concentration for inhalational agents of 0.57 vs 0.93 respectively, dependent on mode of anaesthesia used. In other words, there was a significant difference in the anaesthetic dose between the pEEG group and the usual care group. This suggests that the success of pEEG-guided anaesthesia in these early studies may partially be due to the lower dose of anaesthetic agent in the pEEG group. More recently conducted RCTs suggest that the use of pEEG was not associated with a reduced incidence of POD[5, 151]. A closer read of findings revealed that although there was a slightly lower minimum alveolar concentration in the pEEG group, the difference is not clinically significant. This is important as it may demonstrate that as our understanding of the impact of anaesthetic dose on the older brain has improved; anaesthetists are tending to give a more conservative anaesthetic even in the absence of pEEG guidance. Subsequent meta-analyses have suggested that in the current era of anaesthetic practice, pEEG guidance does not reduce the risk of POD[152, 153].

Burst suppression

Burst suppression is the occurrence of alternating epochs of isoelectric EEG and short bursts of high voltage activity (Figure 1.6). Intraoperative factors known to trigger burst suppression include high anaesthetic dose, hypothermia, hypotension, hypoxia and hypoglycaemia. Several researchers have demonstrated an association between the occurrence of burst suppression during surgery and subsequent POD[154, 155]. Others found that a longer duration of burst suppression was associated with the incidence of POD[156, 157]. However, in all the studies reviewed, a large proportion of participants who experienced prolonged periods of burst suppression did not develop POD. Further complicating the picture is the finding that burst suppression was not associated with post anaesthetic cognitive dysfunction in young healthy volunteers[158]. Research suggests that the propensity for burst suppression may be a factor[159]. In Fritz et al's study, burst suppression at a low anaesthetic dose was associated with a higher incidence of POD. An association between susceptibility to burst suppression and low alpha band power has been demonstrated[160]. Alpha band is a narrow band of brain wave activity with a frequency of 8 – 12 hertz (Hz). Lower intraoperative alpha band power is associated with low preoperative cognitive function[161]. It may be that propensity for burst suppression and low alpha power during anaesthesia are pEEG markers of the vulnerable brain.

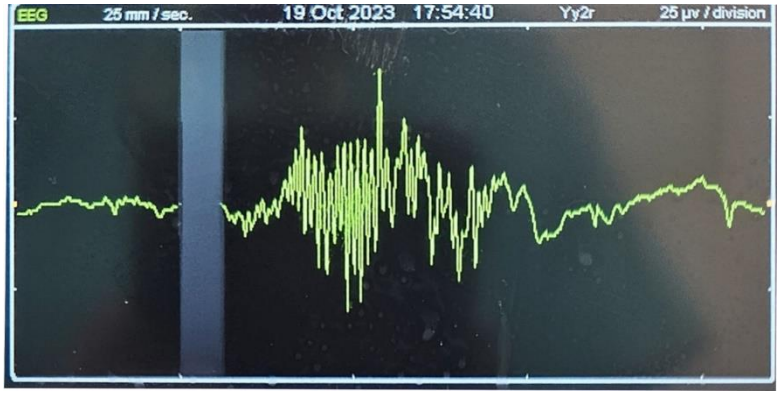

Figure 1.6: Burst suppression on a processed EEG monitor

That said, a lot of the early research focussed on depth of anaesthesia index and burst suppression in the exploration of the role of pEEG-guided anaesthesia in POD risk. There are a few other parameters that the pEEG monitor provides which are now the subject of research. Modern pEEG monitors display the digital spectral array, power spectrum and raw EEG providing us the opportunity to explore brain-wave activity and intrinsic brain vulnerability. Of particular interest is the posterior dominant rhythm (PDR). The PDR is the dominant waveform over the occipital region when subject is resting, not asleep, with the eyes closed. This waveform has a frequency range in the alpha band range i.e. 8 – 12 Hz in adults. As described above, the PDR power may be reduced in the presence of

neurodegeneration. If the PDR can be measured using the processed EEG monitor, there is the potential of exploring it as a biomarker of neurodegeneration.

Electroencephalography during delirium and POD

Incidentally, some researchers advocate the use of postoperative EEG monitoring as a tool for detecting onset of POD. An early study compared the EEG features of older people with hyperactive delirium to age-matched controls[162]. The delirium cohort was a mix of people ranging from no overt cognitive impairment to dementia. The duration of delirium correlated with the relative delta band power in their study. In addition, the relative alpha band power was reduced in delirium compared to age-matched controls. The EEG changes were more significant in participants with delirium and cognitive impairment. Another study on postoperative EEG and POD in a cardiac surgery cohort used the processed EEG monitor[71]. In that study, the depth of anaesthesia index and frontal relative alpha power were lower in people during POD compared to controls. The EEG features of hypoactive delirium may be summarised as reduced alpha band power, increased theta power and increased delta power[163].

Potential biomarkers of inflammation

Considering the overview on inflammation as a potential risk factor for POD, identification of a reliable biomarker for inflammation is relevant. The ideal inflammation biomarker would be an objective and easily measured non-invasively or from peripheral blood. The biomarker would reflect inflammaging, given the contribution of extent of inflammaging to baseline inflammatory status, comorbidities and frailty status in older people. The focus on older people is valid due to the increased incidence of POD and its consequences with increasing age. The ideal biomarker would also be demonstrably associated with systemic inflammation as well as having a clearly defined pathway to neuroinflammation, given that neuroinflammation may be the more proximal trigger for POD.

There are a multitude of inflammatory markers measured in clinical practice including C-reactive protein, white cell count, temperature and procalcitonin. However, these measures do not readily have a readily demonstrable pathway to neuroinflammation. Our review of the literature identifies cytokines particularly interleukins as potential biomarkers.

Summary of Chapter

Postoperative delirium in cognitively intact older people may occur because the combination of covert intrinsic brain vulnerability, the baseline inflammatory status and the rise in inflammatory mediators that occurs due to the surgery/anaesthesia intervention breaches a certain threshold. Quantification of these intrinsic vulnerabilities by identifying

relevant biomarkers may enhance the ability to predict POD in cognitively intact older people.

Aim and objectives of thesis

This thesis aims to elucidate the potential biomarkers of intrinsic brain and inflammatory vulnerabilities for the occurrence of postoperative delirium in overtly cognitively intact older people.

The objectives include the following

- Systematic review and meta-analysis of the role of preoperative inflammatory mediators in the aetiology of POD.
- Clinical research on the association between the difference in levels of preselected blood cytokine levels (and modifiers) across surgery and the occurrence of postoperative delirium in cognitively intact older people undergoing hip fracture surgery.
- Clinical research on the association between preoperative levels of preselected blood inflammatory mediators and postoperative delirium. Analysis of the impact of interactions between chosen mediators and relevant modifiers on the incidence of POD will also be assessed.
- Systematic review on the association between retinal layer thicknesses measured using optical coherence tomography and MCI/delirium in overtly cognitively intact older people.
- Pilot study comparing the RNFL thickness of older people recovering from hip fracture surgery who experience POD to those who do not experience POD.
- Feasibility of obtaining awake occipital EEG from a routinely used processed EEG monitor and comparison of total and relative alpha power from the occipital EEG obtained between people who develop POD and those who do not develop POD.

Systematic review: Preoperative inflammatory markers and postoperative delirium chapter

A version of this systematic review is published in the British Journal of Anaesthesia[164]

Background

The neuroinflammatory hypothesis of delirium suggests mechanisms by which systemic inflammation may result in neuroinflammation and delirium[165]. Given the systemic inflammation associated with moderate or major surgery, it comes as no surprise that many researchers have explored a potential association between inflammation and postoperative delirium (POD). This has resulted in a variety of studies of diverse designs such as differences in the medium from which inflammatory mediators' levels were measured (e.g. cerebrospinal fluid (CSF), serum or plasma). Also, the role (if any) of inflammatory mediators has been investigated as a risk/predictor biomarker (i.e. pre-operatively/pre-POD) and/or as a diagnostic biomarker (i.e. during an episode of POD). Given the wide variety of inflammatory mediators, the breadth of coverage in each study is often limited i.e. single inflammatory mediator or panels of mediators, largely without adjustments for interactions between inflammatory mediators.

That said POD is a significant complication of surgery, particularly in older people. The incidence of POD in this age group is 15 – 53%[16]. Risk factors identified thus far include older age, pre-existing cognitive impairment, functional impairment and visual impairment[15]. POD in older people is associated with significant adverse consequences e.g. increased mortality, higher risk of institutionalisation and greater incidence of subsequent diagnosis of cognitive impairment or dementia. To describe the potential scale of the impact of POD, in 2015 23% of the surgical population in England were age ≥ 75 years[166].

The exploration of systemic inflammation (with resulting neuroinflammation) in the aetiology of postoperative delirium is appealing because it may provide potential targets for modulation of perioperative inflammation and perhaps reduce the incidence of POD, if the neuroinflammatory hypothesis is correct. In this context, the varying degrees of inflammaging and microglial activation associated with aging may modify the effect of systemic inflammation as a risk biomarker for POD. As previously described, inflammaging refers to the chronic low-grade inflammation that occurs with aging and microglial activation alludes to the change in baseline state of microglia from resting to primed that occurs in older people. However, there is inter-individual variation in the extent of inflammaging or microglial priming. This suggests that baseline levels of inflammatory mediators may be variably impacted by inflammaging amongst individuals even if they have the same chronological age. The quest for an ideal inflammatory biomarker favours a measure that encompasses inflammaging. Thus, preoperative inflammatory mediator levels may provide a viable biomarker candidate. We therefore reviewed existing literature on preoperative inflammatory mediators and POD to aid the search for a potential biomarker of inflammation as a risk factor for POD.

Objective

A systematic review and meta-analysis of low risk of bias (RoB) evidence on the association between preoperative blood levels of inflammatory mediators and incidence of POD in older people.

Methodology

Protocol registration: Prospero (ID CRD42019159471)

Structure of review: Preferred reporting items for systematic reviews and meta-analysis (PRISMA)[167].

Article eligibility criteria

Original articles published in peer-reviewed journals with low risk of bias were included. Other inclusion criteria were study cohort with a mean age of ≥ 65 years, POD and no POD as grouping variables, and stated method of POD assessment. Inflammatory mediator levels measured from preoperative blood samples and stated timing of preoperative blood sample were also required. Included studies needed to have screened participants for preoperative delirium and excluded them or performed a subgroup analysis of participants without preoperative delirium.

Information sources

Published reviews

Databases were searched for published reviews to identify the existence and scope of recent reviews on preoperative blood inflammatory mediator levels and POD. Databases included in the search were Cochrane database of systematic reviews, database of abstracts of reviews of effects (DARE), Joanne Briggs institute database of systematic reviews and implementation report (JBI), Medline reviews, PROSPERO international prospective register of systematic reviews and PubMed reviews. The search strategy is included in the appendix.

The search for published review articles identified three studies that were pertinent to the current review's question. While useful, there were factors that suggested a new review and meta-analysis of low risk of bias studies was required. The inclusion of studies that I would class as high RoB[168], limitation of included articles to a 2.5-year window[169] and limited number of included articles precluding meta-analysis[124] in the existing reviews informed the decision to conduct this systematic review and meta-analysis. A summary of reviews of interest is included in the appendix.

Current review

Two independent researchers (A.N. and D.A.) searched Medline, PubMed, CINAHL, Embase, Scopus, Cochrane library, PsycInfo and Web of Science for articles using predetermined search criteria. Search criteria were English language articles, published in peer-reviewed journals until January 2021. Email alerts of new relevant articles were also set up with various databases. The references of selected articles and reviews were searched for further relevant studies.

Search strategy

Various terms regarding postoperative delirium and inflammatory mediators using the relevant medical subject headings (MeSH) and Boolean operators and were used in the relevant databases. Full details of the search strategy are included in the appendix.

Study selection

The articles retrieved from the database searches were screened to identify studies that fulfilled the inclusion criteria.

Analysis of low RoB studies was performed. For comparison, the RoB analysis of all identified articles on preoperative inflammatory mediators and POD irrespective of RoB status is included in the appendix. The focus of this chapter is the review and meta-analysis of the low RoB articles. The flow chart of the study selection process is included below (figure 2.1).

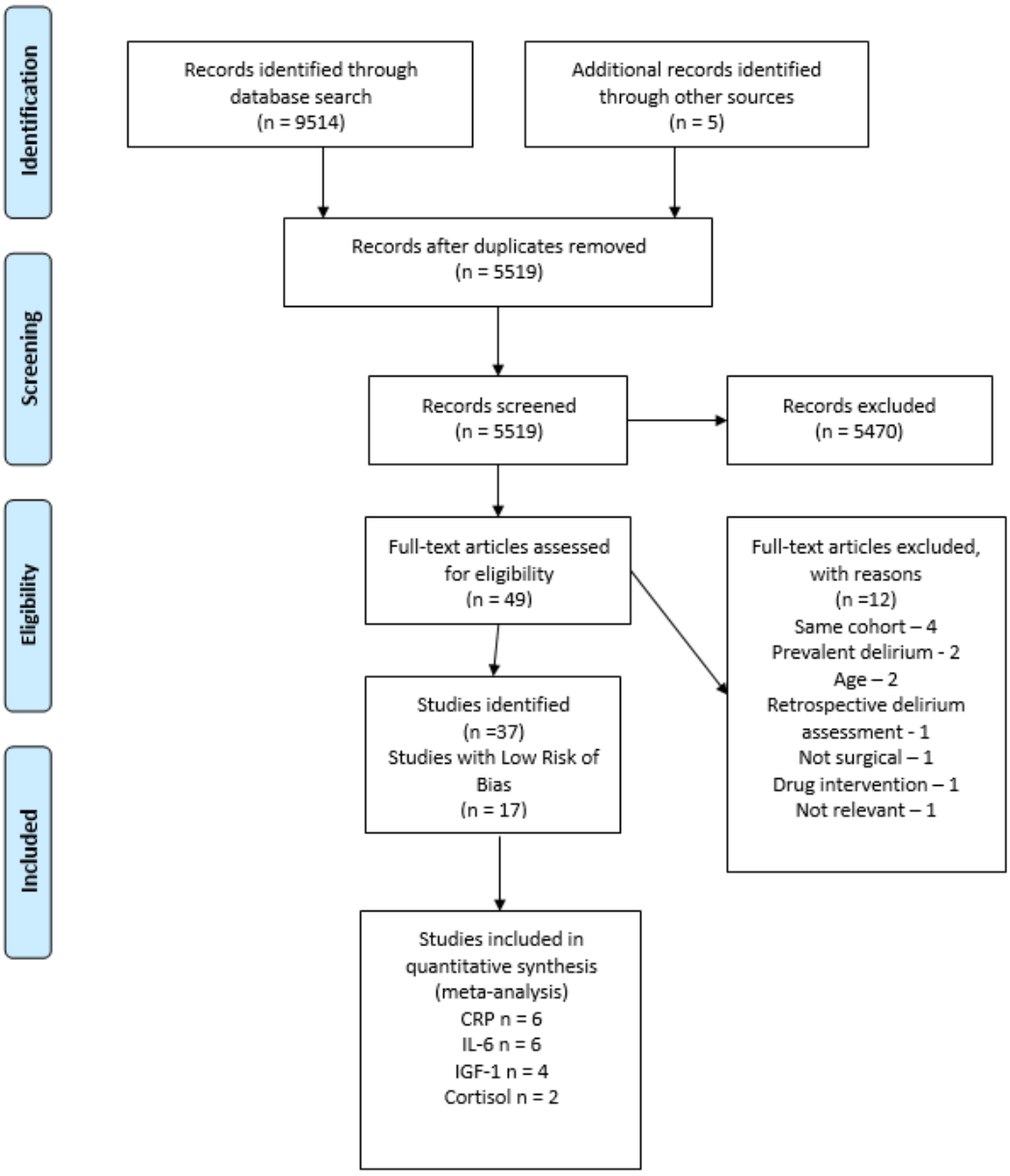

Figure 2.1: Article selection flow chart

Same cohort means two articles on the same cohort

CRP = C-reactive protein, IGF-1 = Insulin-like growth factor-1, IL-6 = Interleukin-6

Data collection

Two researchers (A.N. and D.A.) collected the data items for the review using a piloted form.

Data items

Data items were collected under the subheadings article's characteristics, participants' information, delirium outcomes, blood processing (timing and mode), inflammatory mediators reported values, statistical analysis including confounders. Details of the data items collected are in the appendix.

Risk of bias in individual studies

Risk of bias in the individual articles was assessed using the quality in prognostic studies (QUIPS) tool[170]. Standard domains in the QUIPS tool include study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The QUIPS tool was used to appraise the selected studies independently by three investigators (A.N., D.A., and R.E.). Articles with 'uncertain' in more than one domain were exclude from the low risk of bias review. Studies in which there was uncertainty in the domain of outcome measurement or prognostic factor measurement were also excluded from the low RoB review.

The most frequent source of bias was unclear/unstated interval between preoperative blood sample and surgery[171-173]. Other factors that informed exclusion were greater than 10% withdrawal after recruitment[174], unclear dementia screening[175], retrospective delirium assessment on weekends and differential corticosteroid use [176], unclear or unstated screening for preoperative delirium[177], absence of subgroup values[178] and unclear method of blood processing[179].

Summary measures

Standardised mean difference (SMD) of preoperative mediator levels.

Risk of bias across studies

Funnel plots for each inflammatory mediator were visually inspected to assess publication bias. However, because there were less than 10 studies for most mediators, the interpretation of the funnel plots is of limited value[180]. Funnel plots for mediators in articles irrespective of RoB are included in the appendix.

Synthesis of results and additional analysis

The findings for each inflammatory mediator were summarised. Meta-analyses were performed for each mediator that had an appropriate amount of data available.

To accommodate the nuances of some specialties and urgency of surgery, subgroups (non-cardiac surgery, hip fracture surgery and cardiac surgery) and urgency (elective, emergency or mixed) were embedded in the meta-analyses.

Considering the association of concurrent dementia with incidence of postoperative delirium, a subgroup meta-analysis of cohorts that excluded participants with dementia was performed, where there were available data.

Review manager 5.3 (RevMan 5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and R Platform version 3.5.2 using Meta package (R foundation for statistical computing, Vienna, Austria) were used to conduct the meta-analyses.

To accommodate unobserved heterogeneity and support generalizability of findings, a random effects model was used. The measure of effect size was SMD with 95% confidence interval (CI). Heterogeneity was assessed using Higgin's I^2 measure.

In studies where values were reported as median and interquartile range (IQR), we used Luo and Wan's method to convert to mean and standard deviation (SD)[181, 182]. Results reported as mean and standard error (SE) were converted to mean and SD by multiplying the SE by the square root of the sample size.

Results

Database search yielded 9514 articles and a further 5 articles were identified from other sources such as article references and database notifications. After exclusion of duplicate publications, publications not relevant to review, non-human studies, CSF studies, studies on postoperative inflammatory mediator levels, and review articles, there remained 49 articles that were potentially eligible. Further screening highlighted studies on the same cohort, prevalent delirium, younger participants, and drug intervention studies resulting in 37 studies for the review. Our RoB assessment identified 17 articles as having low RoB (figure 2.1).

Incidence of postoperative delirium

Across the studies included in this review, the incidence of POD was median (IQR) 24% (21 – 32).

Study Characteristics

Characteristics of the studies included are depicted in Table 2.1

Author	Year	Type of study	Type of surgery	Number with POD	Number without POD	Mean age POD	Diagnostic tool for POD	Incidence of POD	Inflammatory mediator
Osse	2012	Case control	Elective cardiac	58	67	76.7 +/- 3.9	CAM-ICU	31.34%[a]	CRP Neopterin
Shen	2016	Cohort	Elective gastrointestinal tumour resection	36	104	73.8 +/- 5.9	CAM and DRS	25.71%	CRP IL-6 IGF-1
Guo	2016	Cohort	Hip fracture	120	452	82 (IQR 76 – 86)	CAM	20.98%	CRP
Slor	2019	Cohort	Hip fracture	41	80	85.4 +/- 5.6	CAM	33.88%	CRP
Lemstra	2008	Case control	Hip joint	18	50	80 (Range 71 – 91)	DRS	NA	CRP IL-6 IGF-1
Cerejeira	2012	Cohort	Elective hip joint	37	64	73.6 +/- 5.9	CAM	36.63%	CRP TNF-α IL-6 IL-8 IL-10
Vasunilashorn	2017	Cohort	Elective non-cardiac	134	426	77.5 +/- 5.0	CAM	23.93%	CRP
Sun	2016	Case control	Oral cancer	56	56	73.2 +/- 6.5	CAM	21.79%[a]	CRP IL-6
Chen	2019	Cohort	Elective cardiac	85	181	67 +/- 7.7	CAM-ICU	32%	IL-6
Vasunilashorn	2015	Case control	Elective non-cardiac	75	75	77.3 +/- 5	CAM	NA	IL-6 IL-8 IL-10 TNF-α
Liu	2013	Cohort	Elective non-cardiac	50	288	74 +/- 6	CAM-ICU	14.8%	IL-6
Capri	2014	Case control	Any kind of elective or emergency surgery	37	37	79.2 +/- 6.7	CAM	NA	IL-6 IL-8 IL-10
Peng	2019	Cohort	Elective hip and knee arthroplasty	55	217	74.5 +/- 5.6	DSM 5	20.2%	IGF-1 TNF-α
Cerejeira	2013	Cohort	Elective hip joint	37	64	73.6 +/- 5.9	CAM	36.63%	IGF-1 Cortisol
Chu	2016	Cohort	Vertebral hip or knee	23	80	81.13 +/- 5.05	CAM	22%	IGF-1
Kazmierski	2013	Cohort	Elective cardiac	41	72	68.6 (IQR 64 – 74)	CAM-ICU	36%	Cortisol
Koftis	2019	Cohort	Elective cardiac	129	839	65.37 +/- 7.77	CAM-ICU	13.3%	CRP

Table 2.1: Characteristics of articles included in the preoperative inflammatory mediators and POD review

CAM, confusion assessment method; CRP, C-reactive protein; DRS, delirium rating scale; IGF-1, insulin-like growth factor 1; IL, interleukin; TNF-α, tumour necrosis factor alpha.

Risk of bias within studies

This was assessed using the QUIPS tool. The performance of the studies selected for this review is depicted in figure 2.2 and 2.3.

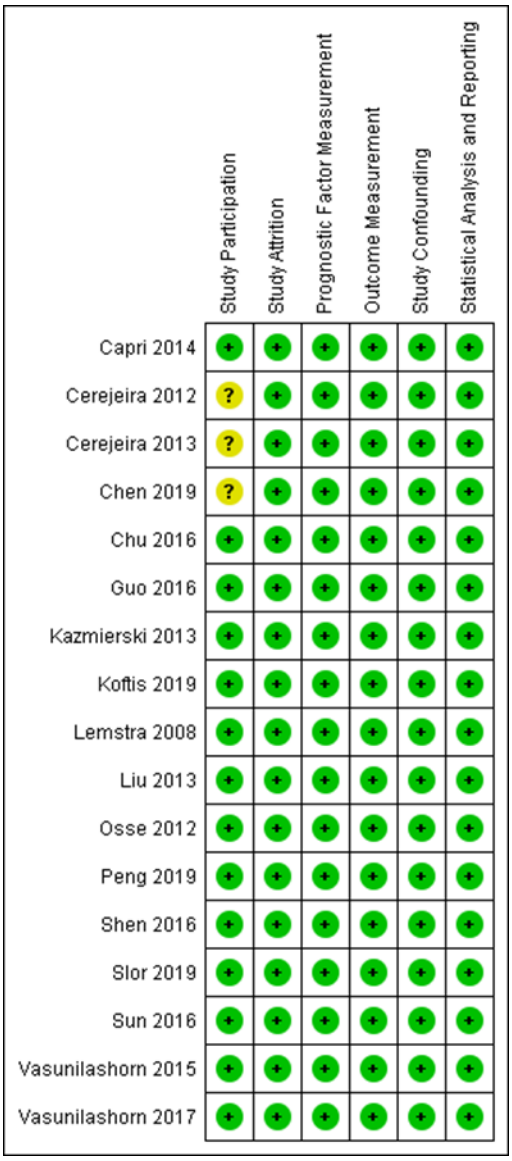

Figure 2.2: Risk of bias summary of studies included in the preoperative inflammatory mediators and POD review.

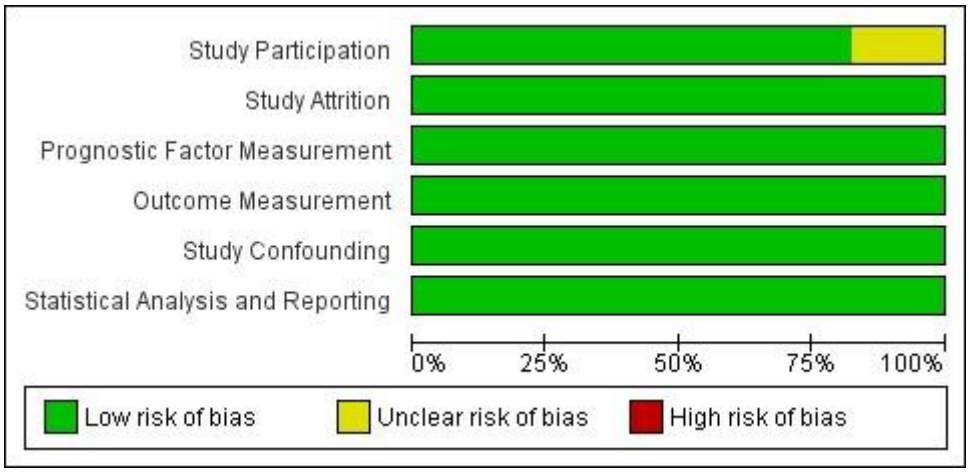

Figure 2.3: Risk of bias graph of articles included in the preoperative inflammatory mediators and POD review.

Analysis of individual inflammatory mediators

Preoperative C-reactive protein and postoperative delirium

There were nine studies on the association between preoperative CRP and POD[1, 80, 125, 183-188]. Recruitment patterns were consecutively recruited cohort in six and case-control in three.

POD assessment - CRP

There was a wide variability in the delirium assessment tool used across studies (Figure 2.4)

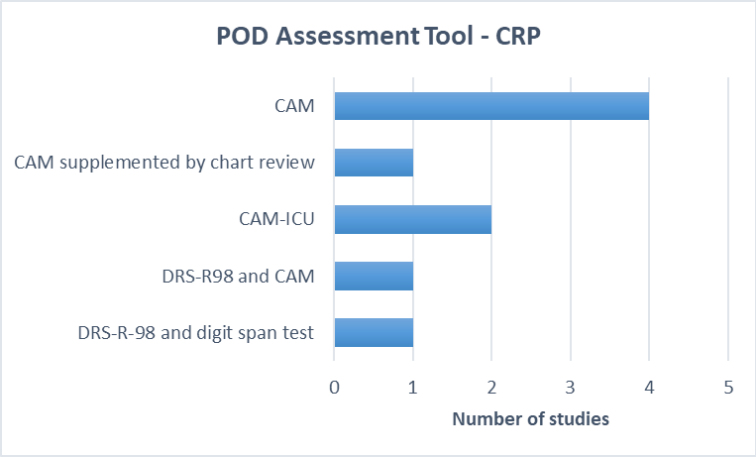

Figure 2.4: POD assessment tools used in CRP studies

CAM-ICU= Confusion assessment method for intensive care unit

DRS-R-98 = Delirium rating scale revised 1998

POD assessments were performed by a variety of personnel including psychiatrist, trained researcher, study staff adjudicated by delirium experts, trained researcher confirmed by a psychiatrist, geriatrician, expert in psychology, anaesthetist, and clinical team.

POD assessments were also of varying intervals and duration including daily, daily from postoperative days 1 – 3, daily from postoperative day 1 – 5, daily from postoperative day 2 – 7, daily from postoperative day 1 until discharge, twice daily from postoperative day 1 -3 3, twice daily on postoperative day 2 and 3, and twice daily for 6 days postoperatively.

Preoperative blood samples - CRP measurement

The interval between acquisition of blood sample and surgery also varied across studies (Figure 2.5). The medium from which CRP was measured was serum in two studies, plasma in five studies and blood (not further specified) in two studies.

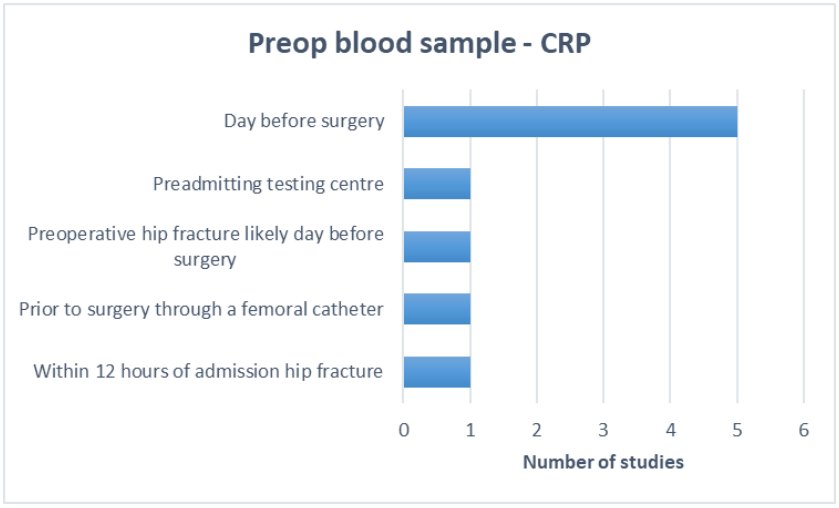

Figure 2.5: Interval between preoperative CRP sample and surgery.

Summary of findings - preoperative CRP and POD

There was an association between higher preoperative CRP levels and increased incidence of POD in five studies[80, 125, 183, 184, 187]. Multivariate analysis confirmed that high CRP was an independent risk factor for POD in two studies[184, 187].

Meta-analyses - preoperative CRP and POD

Six studies had sufficient data for inclusion in a meta-analysis[1, 80, 125, 183-185]. There were 1991 participants of whom 402 had POD. Random effects model was used.

Preoperative CRP was not significantly different between people who developed POD and those who did not develop POD. The SMD was 0.42 (95% CI -0.19 to 1.04, p = 0.18). However, there was significant heterogeneity demonstrated by an I^2 of 96%. Figure 2.6.

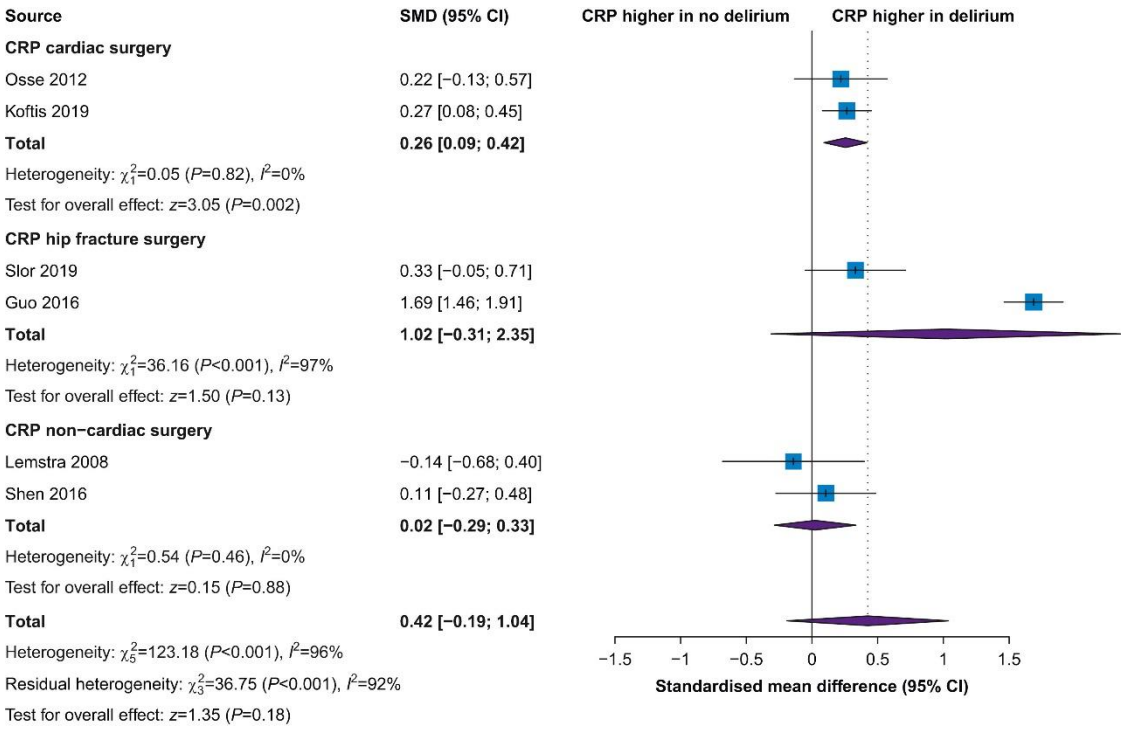

Figure 2.6: Forest plot of association between preoperative C-reactive protein and postoperative delirium

Subgroup analysis was performed to identify if there were any specialty specific associations. Surgical specialty classification included cardiac surgery, hip fracture surgery and non-cardiac surgery. In the cardiac surgery subgroup, there was an association between preoperative CRP levels and subsequent POD (SMD 0.26, 95% CI 0.09 to 0.42, p = 0.002). The result of this analysis is embedded in figure 2.6.

A funnel plot was inspected to assess for publication bias (figure 2.7). Given the paucity of studies available, no conclusions were draw from the plot.

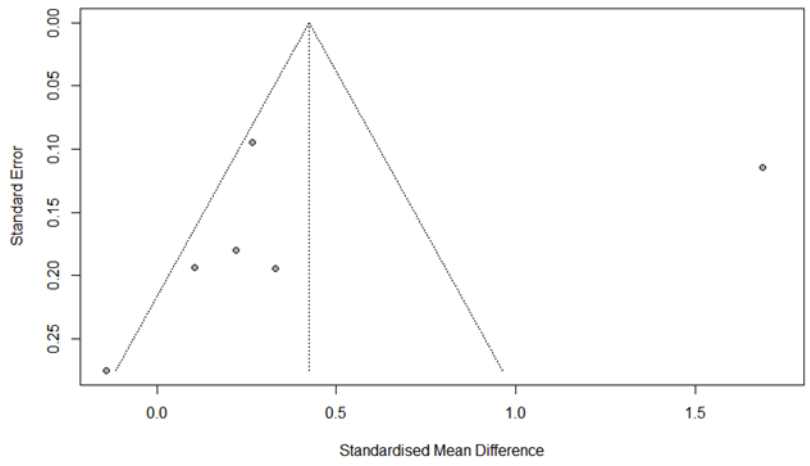

Figure 2.7: Funnel plot of studies included in analysis of preoperative CRP and POD

In keeping with our a priori plan, a meta-analysis was conducted on a subset of patients that did not have concurrent dementia. There were four studies included in this analysis[80, 125, 184, 185]. There were 1797 participants of whom 326 experienced POD. A random effects model was used.

There was no association between preoperative CRP levels and postoperative delirium (SMD 0.60, 95% CI -0.21 to 1.42, p = 0.15). An I^2 of 97% also indicates severe heterogeneity in this analysis. (Figure 2.8)

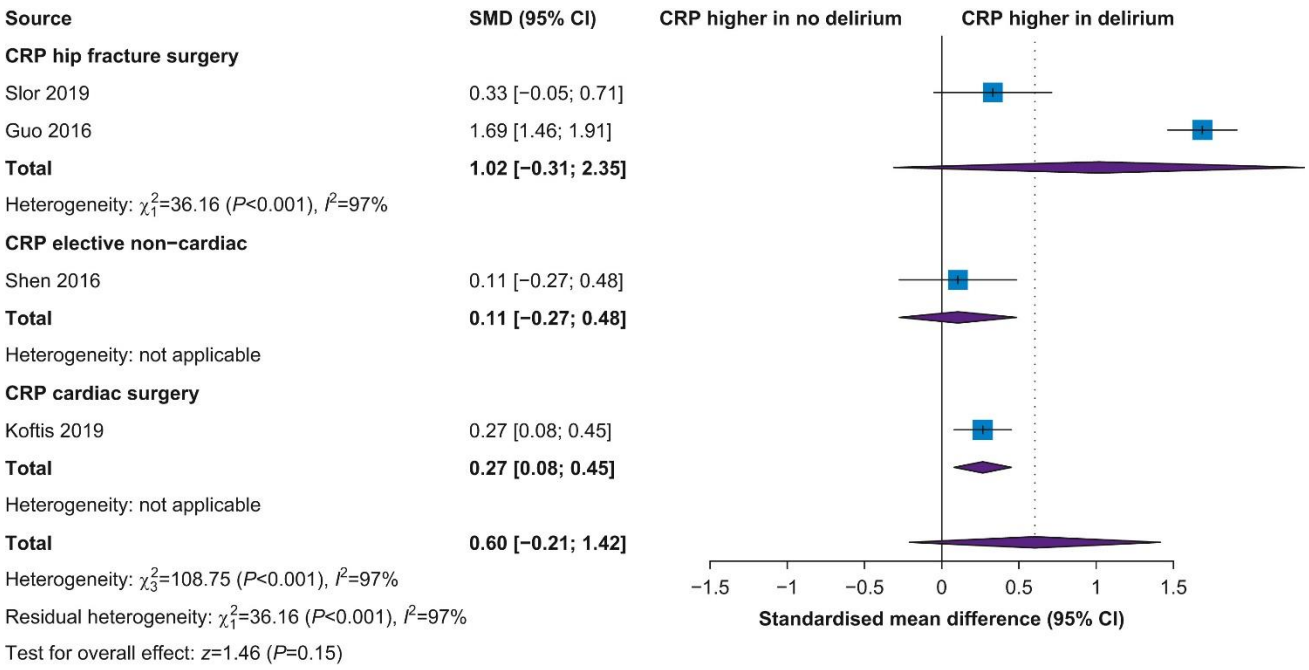

Figure 2.8: Forest plot of preoperative CRP in people without concurrent dementia and subsequent POD.

Preoperative interleukin-6 and postoperative delirium

Nine studies explored an association between preoperative interleukin-6 (IL-6) and POD[1-3, 31, 80, 186, 188-190]. Participant recruitment patterns were consecutive in four[3, 80, 186, 189], case-control in four and prospective (not further characterised) in one study[190].

POD assessment – IL-6

A variety of tools were used to diagnose POD (figure 2.9)

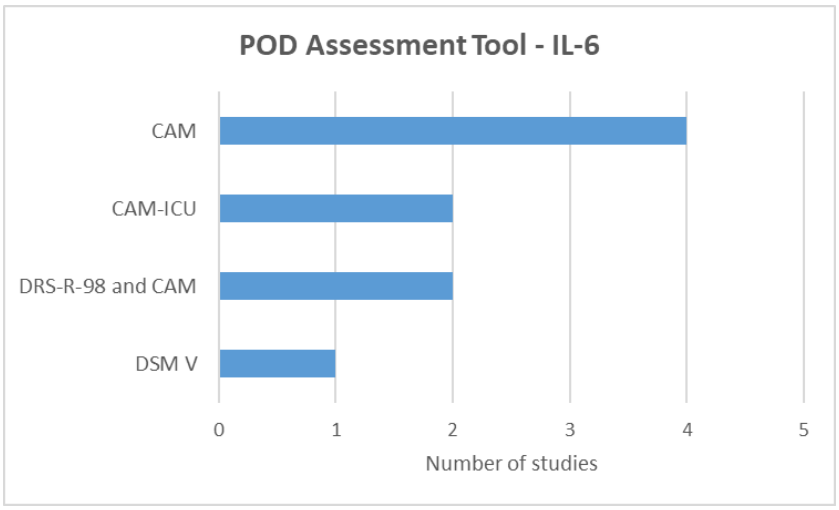

Figure 2.9: POD assessment tools used in the IL-6 studies

Delirium assessments were performed by researchers, study staff adjudicated by delirium experts, expert in psychology, psychiatrists, trained researcher confirmed by psychiatrist, clinical researchers with medical or psychological training, and trained assessors.

Frequency of POD assessment varied across studies. They included daily, daily for the first seven days after surgery, daily on postop days 1,2,3 and 6, daily for the first 3 days after surgery, twice daily on postoperative days 1 to 3, twice daily on postoperative days 2 to 3, and twice daily for the first five days after surgery.

Preoperative blood sample - IL-6 measurement

The time interval between obtaining the preoperative blood sample from which IL-6 was measured and time of surgery varied from study to study (figure 2.10)

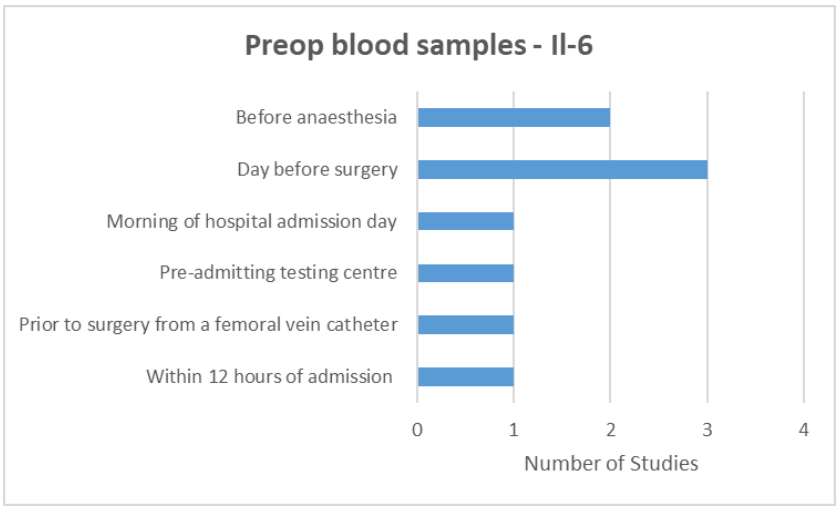

Figure 2.10: Interval between preoperative blood sample for IL-6 measurement and surgery.

IL-6 was measured from serum in four studies, plasma in 4 and blood (not further specified) in one.

Assay kits used for IL-6 were IL-6 enzyme-linked immunosorbent assay (ELISA) kits in six studies[1, 3, 80, 188-190] and multiplex assays in the remaining three studies.

Summary of findings - preoperative IL-6 and POD

Three studies demonstrated an association between preoperative IL-6 and POD[2, 3, 80] while six studies did not.

Meta-analyses - preoperative IL-6 and POD

Six studies had sufficient data for inclusion in a meta-analysis[1-3, 80, 189, 190]. Across the six studies, there were 1,155 participants of whom 281 had POD. Heterogeneity was moderate based on an I^2 of 58%.

In this meta-analysis higher preoperative IL-6 was associated with subsequent POD (SMD = 0.33, 95%CI 0.11 to 0.56, p = 0.003) (figure x).

Subgroup analysis was performed using type of surgery as the grouping variable. The subgroups (number of studies) were cardiac surgery (1 study), elective non-cardiac surgery (3 studies) and mixed cardiac surgery (2 studies). The results of this analysis are embedded in figure 2.11.

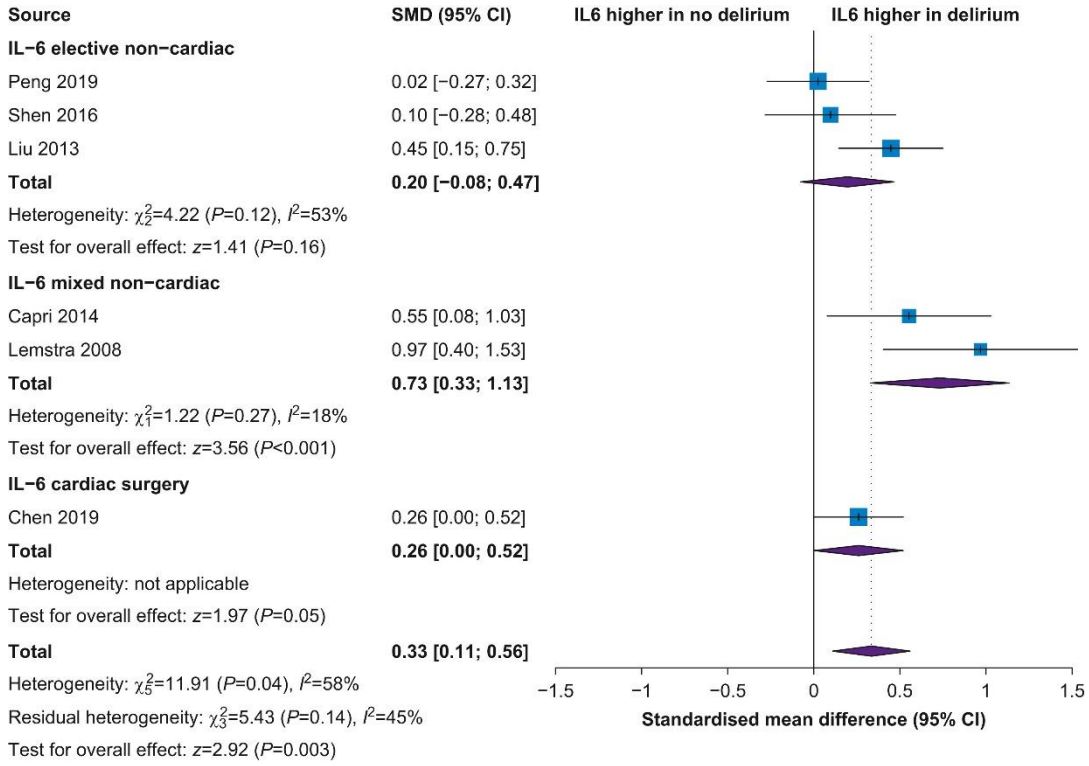

Figure 2.11: Forest plot of preoperative IL-6 and POD

To assess for publication bias a funnel plot was graphed (figure 2.12). Given that the meta-analysis included less than 10 studies, the plot should be interpreted with caution.

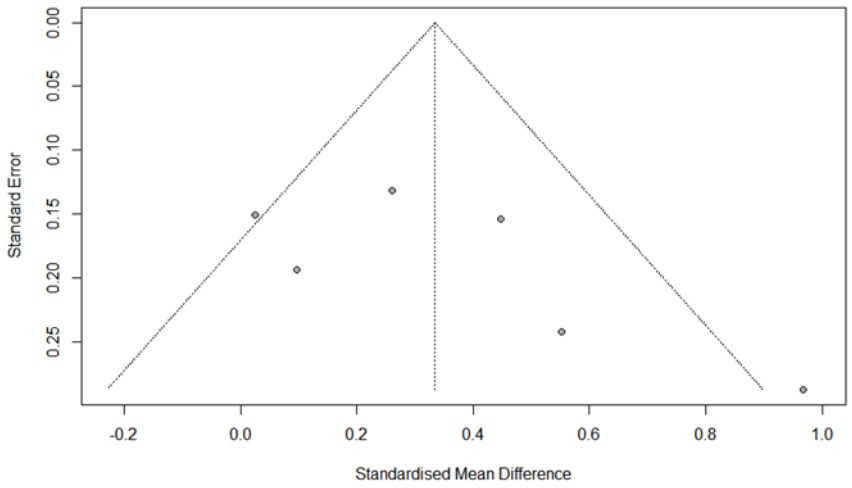

Figure 2.12: Funnel plot on studies included in meta-analysis of preoperative IL-6 and POD

A further meta-analysis, on preoperative IL-6 and POD, was conducted that included studies with data on participants without concurrent dementia. There were four studies in this analysis[2, 3, 80, 190] which included 821 participants of whom 178 had POD.

There was an association between high preoperative IL-6 and POD in this meta-analysis (SMD 0.26, 95% CI 0.01 to 0.51, p = 0.04). Heterogeneity was moderate based on an I^2 of 51% (figure 2.13).

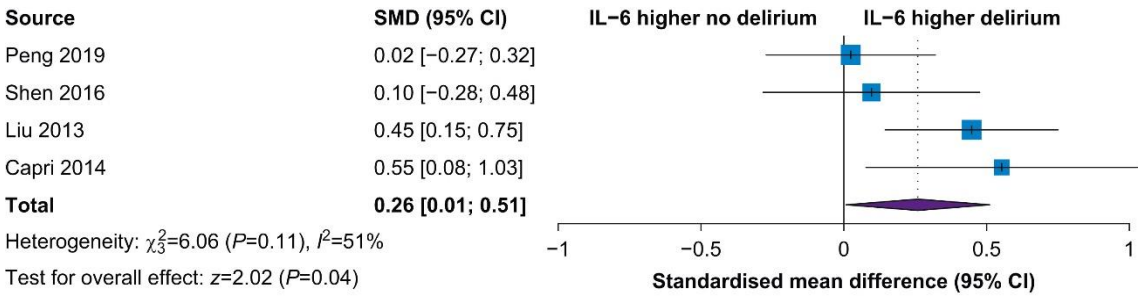

Figure 2.13: Forest plot of Preoperative IL-6 and POD in older hip fracture patients without dementia.

Preoperative interleukin 8/interleukin 10 and POD

Identified studies on preoperative IL-8 and post POD also reported on IL-10 and POD.

There were three low RoB studies of which two were case-control design and the remaining study was consecutive cohort[2, 31, 186].

POD assessment – IL-8 and IL-10

Trained researchers, trained researchers adjudicated by at least two delirium experts and a psychiatrist performed POD assessments.

Assessments were performed daily of postoperative days 1 – 3 in two studies and daily on postoperative days 1 -3 and day 6 in the third study.

The confusion assessment method (CAM) was used in all three studies.

Preoperative blood sample - IL-8 and IL-10 measurement

The intervals between preoperative blood samples and surgery also varied between studies. The timing with respective to surgery were as follows.

- Pre-admitting testing centre
- Day before surgery
- Morning of hospital admission

All three studies measured IL-8/IL-10 from plasma using multiplex assay.

Summary of findings - preoperative IL-8/IL-10 and POD

Two studies were on elective, non-cardiac surgery and the third study recruited a mixture of elective and emergency cases. One of the studies found an association between preoperative IL-8 and POD in their discovery cohort but this was not replicated in the pooled (larger) cohort.

Overall, there was no association between preoperative IL-8/IL-10 levels and the incidence of POD.

There was insufficient available data to conduct a meta-analysis.

Preoperative tumour necrosis factor alpha (TNF-α) and POD

There were three low RoB studies on an association between preoperative TNF-α and POD of which two were consecutive cohort and one was case-control[3, 31, 186].

POD assessment – TNF-α

Tools used for delirium assessment were CAM in two studies[31, 186]. In the third study, a psychiatrist using DSM-V criteria performed POD assessments.

In the studies where CAM was used, the assessors were psychiatrist and trained researchers.

POD assessments were performed daily for the first three postoperative days in two studies. The third study performed daily POD assessments during the first seven postoperative days.

Preoperative blood sample - TNF-α

Interval between preoperative blood samples for TNF-α and surgery were as follows

- Day before surgery – two studies
- Pre-admitting testing centre

TNF-α levels were measured from plasma in two studies and serum in the third study. Assay kit was multiplex in two studies and TNF-α ELISA in the third study.

Summary of findings - preoperative TNF-α and POD

All studies were on elective, non-cardiac surgery patients. None of the studies identified an independent association between preoperative TNF-α and POD.

There was insufficient data available to conduct a meta-analysis.

Preoperative insulin-like growth factor 1 (IGF-1) and POD

An association between preoperative IGF-1 and POD was investigated in four studies[1, 72, 80, 191]. They were all prospective studies of which one was case-control.

POD assessment – IGF-1

The POD assessment tool employed was CAM in all studies. However one of the studies also used DRS[80].

Trained researchers confirmed by a psychiatrist (two studies), trained researchers and a psychiatrist performed POD assessments.

Assessments were performed daily for an unspecified duration in two studies, daily on postoperative days 1 – 3, and daily on postoperative days 2 and 3.

Preoperative blood samples - IGF-1

Preoperative blood samples were obtained within 12 hours of admission in one study and on the day before surgery in the remaining three studies.

Blood component assayed was serum in two studies, plasma in one study and unspecified in the fourth study.

All the studies used IGF-1 ELISA assays.

Summary of findings - preoperative IGF-1 and POD

Preoperative IGF-1 was inversely related to the incidence of POD in one study[80]. There was no association between preoperative IGF-1 and POD in the other three studies.

Meta-analysis - preoperative IGF-1 and POD

All four studies were included in the meta-analysis. There were 412 participants of whom 114 developed POD.

There was no association between preoperative IGF-1 and POD in this analysis (SMD = -0.009, 95% CI –0.13 to 0.31, p = 0.79) (figure 2.14).

The I^2 suggests an absence of significant heterogeneity.

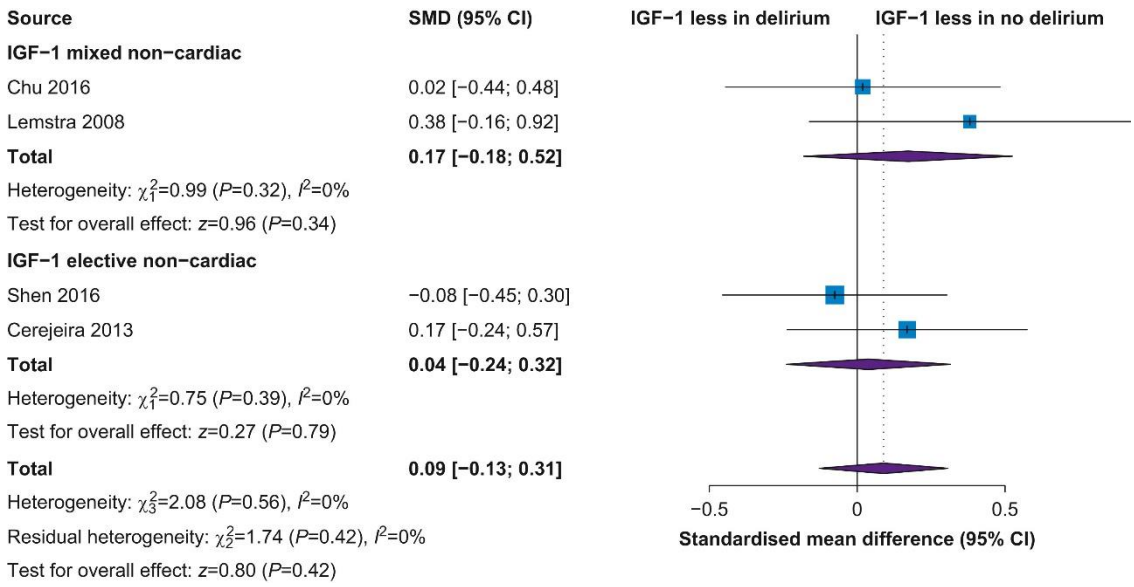

Figure 2.14: Forest plot of preoperative IGF-1 and POD

Preoperative cortisol and POD

Three studies explored the association between preoperative cortisol and POD[72, 188, 192]. Recruitment patterns were consecutive cohort in two studies and case-control in the third study.

POD assessments – Cortisol

Two of the studies used CAM tool while the third used CAM-ICU to assess for POD.

A psychiatrist in two studies and an expert in psychology conducted these assessments. Frequency of POD assessments were as follows

- Daily from postoperative days 1 to 3
- Twice daily from postoperative days 1 – 3
- Twice daily from postoperative days 1 to 5

Preoperative blood sample - cortisol

Timing of blood samples from which cortisol was measured was stated as

- Before surgery
- Between 08:00 and 09:00 on the day before surgery
- Morning of the day of surgery

Cortisol was measured from plasma in two studies and serum in the third study.

Assay methods were ELISA, electrochemiluminescent enzyme immunoassay and immunoassay (not further specified).

Summary of findings - preoperative cortisol and POD

Two studies were on elective, non-cardiac surgery and one was on cardiac surgery patients. There was an association between preoperative cortisol levels and POD in one study. There was no association in two studies.

Meta-analysis - preoperative cortisol and POD.

Two studies had sufficient data to support a meta-analysis. There were 214 participants of whom 78 developed POD. In this analysis, there was no association between preoperative cortisol and POD (SMD = 0.16, 95% CI -0.68 to 1.00, p = 0.71) (figure 2.15).

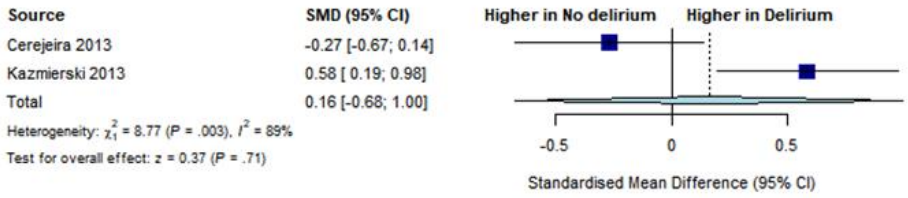

Figure 2.15: Forest plot of preoperative cortisol and POD

Preoperative neopterin and POD

Neopterin, produced by macrophages activated by gamma interferon, is a marker of immune stimulation[193]. It is included in this discussion because the literature search identified three studies on preoperative neopterin levels and POD. Unfortunately, only one fulfilled the low RoB requirement of this review[183].

An investigator or psychiatrist using the CAM-ICU tool performed delirium assessment.

Neopterin was assayed from plasma taken the day before surgery. High performance liquid chromatography was used.

There was an association between higher preoperative neopterin levels and POD.

Discussion of preoperative inflammatory mediators and POD

In this review, there was an association between preoperative IL-6 levels and POD. The subgroup analysis, which excluded people with dementia, also demonstrated an association between preoperative IL-6 and POD. The latter finding is important in light of the association between inflammaging and Alzheimer's disease, a common cause of dementia[194]. Overt neurodegeneration i.e. dementia and MCI are risk factors for the development of POD. Given this, the finding that higher preoperative IL-6 levels may be associated with higher incidence of POD in people without dementia suggests that IL-6 may be an independent association with POD.

In cardiac surgery patients, higher preoperative CRP may also be associated with an increased incidence of POD. Although there were only two studies in this analysis, the absence of significant heterogeneity (I^2 of 0%) supports this finding. In other surgical groups, there was no association.

The only low risk of bias study on preoperative neopterin levels and POD suggests an association.

Surprising is the lack of association between preoperative IGF-1 levels and POD. A study on acute medical patients, age ≥75 years found an inverse relationship between admission levels of IGF-1 and delirium[195]. Given the neuroprotective and neurotrophic properties of IGF-1, there was an expectation of an inverse relationship between the preoperative levels of IGF-1 and POD. There are a few possible conclusions from this. It may be that there is no association between preoperative IGF-1 and POD as determined by the findings of this review. Alternatively, there may be an unmeasured moderator. IGFBP-3 is a major binding protein for IGF-1 (see introduction chapter). An exploration of the dynamics between IGF-1 and IGFBP-3, in the first instance may provide some answers.

There was no association between IL-8, IL-10, TNF-α or cortisol and POD.

Although this review has gone some way in clarifying the role of preoperative inflammatory mediators in POD in older people, particularly IL-6, there remain areas of uncertainty.

Some contributors to this uncertainty include the variety in conduct of POD assessment, differences in surgical procedure and cytokine dynamics.

POD is an acute condition that fluctuates over the course of the day[16] and occurs in hospital up to 1 week after surgery[196]. This suggests that accurate capture of the incidence of POD requires several assessments during the course of the day, for 7 days after surgery. Given the frequency and duration of POD assessments in the included studies, there is the potential that some instances of POD were missed.

Regarding the nature of surgery, the nuances of cytokine surge associated with different approaches to surgery (as discussed in the introduction) are all too apparent. Laparoscopic cholecystectomy and open cholecystectomy are both non-cardiac surgery; however, they induce disparate scales of cytokine activation[46]. Hip fracture patients are a particularly unique subgroup. The trauma that caused the hip fracture and the process of fracturing may

have induced the inflammatory response. The baseline, innate levels of inflammaging in the individual patients is therefore unknown and the preoperative cytokine levels in these patients serves as an assessment of inflammatory response to the injury. Perhaps, a study of the relative increase in cytokines due to the surgery/anaesthesia intervention may enhance our understanding of POD risk in these patients.

In addition, some surgical specialties have unique factors that may contribute to the risk of POD. For example, cardiac surgery, utilising a cardiopulmonary bypass circuit, has associated cytokine activation due to contact of blood with the circuit[197]. Furthermore, the adverse neurological effects of cerebral microembolism due to aortic cannulation and manipulation are well described[198].

The handling of cytokines is also problematic. As discussed in the introduction chapter, cytokines do not act in isolation. Rather there is a myriad of interactions between cytokines, e.g. potentiation or inhibition, making the analysis of individual cytokines, in isolation, superficial and probably flawed. Some authors have attempted to compensate by using an 'inflammatory score', i.e. the ratio between pro-inflammatory and anti-inflammatory cytokine levels[2, 186]. While the motivation is appreciated, this remains unsatisfactory as it implies equal weighting for each unit of cytokine involved. Adding to the complexity of developing an inflammatory/cytokine score is the pleiotropic (anti- and pro-inflammatory) property of IL-6 and TNF-α[48, 57]. A further factor to consider is the interaction of cytokines with soluble receptor, e.g. IL-6 and sIL-6R, or binding proteins, e.g. IGF-1 and IGFBP-3.

Timing of blood samples prior to surgery also varied across the studies. A study compared the association between preoperative CRP taken ≤ 1 day before surgery and POD vs CRP taken up to 7 days before surgery and POD incidence[199]. In their analysis, CRP taken up to seven days before surgery was not associated with the incidence of delirium whereas for CRP taken ≤ 1 day before surgery, there was an association between preoperative CRP levels and POD. This study highlights the importance of the temporal relationship between the preoperative blood sample and surgery.

Despite these challenges, our findings support the hypothesis that systemic cytokines may contribute to the risk of POD therefore providing support for the neuroinflammatory hypothesis of delirium. However, more research is required to validate our findings and identify potential targets for intervention. To achieve this, a more standardised approach to investigating cytokines in POD must be agreed.

In the published version of this work, a case was made for experts in the field to formalise a consensus guideline on the minimum datasets required in the investigation of POD, especially concerning cytokines and other blood biomarkers. This would minimise the uncertainty described above.

As a minimum, this researcher suggests

- POD assessments
  - All studies use the same POD assessment tool except in special circumstances such as ventilated patients and the cognitively impaired

- POD assessments occur at least twice a day (approximately 12 hourly) or preferably three times a day (approximately 8 hourly)
- POD assessments are prospective
- Minimum duration of POD assessments should be postoperative day 1 – 5 (preferably day 1 - 7)

- Surgical categories
  - Creation of subcategories that reflect the extent of surgical trauma, e.g. laparoscopic non-cardiac vs open non-cardiac surgery.
- Blood samples
  - Preoperative blood samples to be taken in theatre just before surgery except in special circumstances, e.g. cortisol which has diurnal variation and seasonal variation[200]
  - Postoperative blood samples to be taken at standardised times after surgery
  - Standardise medium for assay, e.g. plasma[201]

The magnitude of cytokines required to induce POD may be influenced by the resilience/vulnerability of the brain. There is evidence that the vulnerable brain e.g. dementia, has an increased risk of developing POD[15]. While this intrinsic vulnerability is obvious in the context of established neurodegeneration, there is currently a dearth of simple bedside tools that may be used to determine or assess for covert neurodegeneration, especially in overtly cognitively intact older people. In our current technological world, the development of such tools may aid our understanding of the interaction between systemic cytokines and intrinsic brain vulnerability in the aetiology of POD.

Systematic review: Optical coherence tomography in mild cognitive impairment chapter

A version of this review is published in Clinical neurology and neurosurgery[202].

Background

In the systematic review on preoperative inflammatory mediators and POD, the concept of simple bedside tools to measure potential biomarkers of covert neurodegeneration in overtly cognitively intact older people was introduced. To identify potential candidates, features associated with established neurodegeneration, e.g. Alzheimer's disease (AD), were explored. AD was chosen because it is one of the most common causes of dementia and has been extensively studied. Significantly, AD has a long preclinical period. On that premise, there is the potential that features associated with AD may be present, albeit to a lesser extent, in overtly cognitively intact older people with covert neurodegeneration.

A potential candidate is the circumpapillary retinal nerve fibre layer (cpRNFL) thickness. The thickness of the cpRNFL reduces with age at an average rate of 0.52µm/year[137]. There is some evidence of accelerated thinning of the cpRNFL in people with neurodegenerative disorders. In AD, and other neurodegenerative disorders such as multiple sclerosis and Parkinson's disease, cpRNFL is thinner than in healthy, age-matched controls[133, 203-206]. Indeed, thinning of the cpRNFL may be associated with brain atrophy in multiple sclerosis[207].

The retina may be segmented into its composite layers and thicknesses of identified layers measured using optical coherence tomography (OCT)[131]. By segmentation, we refer to the demarcation/delineation of each retinal layer. OCT is a non-invasive tool that uses low coherence interferometry to depict cross-sectional images of the retina. The device may be time-domain or, in more modern devices, spectral-domain. Spectral-domain OCT has the advantage of rapid acquisition of high-resolution images.

As highlighted, thinning of the cpRNFL is associated with AD. Given the proposed trajectory of neurodegeneration, i.e. 'no neurodegeneration' to 'overtly cognitively intact with covert neurodegeneration' to 'mild cognitive impairment' then 'overt neurodegenerative disease', the following question arises. Is there an association between thinning of the cpRNFL and mild cognitive impairment (MCI)? This systematic review attempts to answer this question. Given this works proposal that delirium may be an unmasking of intrinsic brain vulnerability in some patients, a review of cpRNFL and delirium was also planned.

Mild cognitive impairment is an umbrella term that encompasses subtypes of cognitive impairment of disparate aetiology and sequelae[208]. Amnestic MCI, as defined by Petersen's criteria has a more predictive association with Alzheimer's disease (about 10 -12%/year conversion rate)[209]. However, a longitudinal study that followed up participants over three years suggests that up to 50% of people with amnestic MCI remained stable during the follow-up period[210]. A longitudinal voxel based morphometry study demonstrated neurodegeneration in progressive MCI. These changes were absent in stable MCI[211]. This suggests that amnestic MCI may also be associated with some heterogeneity. That said,

currently amnestic MCI is the most specific subtype of MCI that is deemed a potential precursor of Alzheimer's dementia.

Objectives

Primary objective: To evaluate the literature on cpRNFL thickness measured using OCT in MCI/delirium.

Secondary objectives: To identify if there is any association between the thicknesses of other retinal layers, e.g. ganglion cell inner plexiform layer (GCIP), measured by OCT and MCI/delirium.

Subgroup analyses on spectral domain OCT, as well as amnestic MCI were performed.

Methods

Protocol registration: Prospero (ID – CRD42019122165).

Structure of report: Preferred reporting items for systematic reviews and meta-analysis guideline (PRISMA).

Eligibility criteria

Original studies published in peer-reviewed journals that compared the retinal layer thicknesses measured with OCT between people with MCI/delirium and healthy controls. While cohorts with a mean age of ≥ 65 years was preferred, we accepted studies that included younger participants if there were age-matched with controls. Selected studies were required to state the method of diagnosis of MCI/delirium, type of OCT device used (time- or spectral-domain) and demonstrate screening for (and exclusion of) other retinal or systemic pathologies that could affect the retinal thickness. Review articles were excluded.

Information sources

Published reviews

Cochrane database of systematic review, database of abstracts of reviews of effects (DARE), Joanna Briggs institute database of systematic reviews and implementation report (JBI), Medline reviews, National institute of clinical excellence evidence (NICE), PubMed reviews and Prospero international prospective register of systematic reviews were searched for relevant published or registered reviews. The search strategy for review articles on OCT and MCI/delirium are included in the appendix.

Our search identified four reviews albeit with conflicting results[203, 204, 212, 213]. These conflicts may have resulted from limited number of studies available, pooling of MCI diagnosed with

diverse criteria, and domain of OCT device used. A summary of identified reviews of interest is included in the appendix.

There were no existing reviews on OCT and delirium.

Current review

A.N. and D.A. independently searched for relevant articles. CINAHL, Cochrane, EMBASE, Medline, PubMed, PsycINFO, Scopus, TRIP and Web of Science were searched for articles published between 1995 and March 2019. The start of the search period was determined by the publication year the Petersen definition of MCI[214]. The references of identified articles were searched for further relevant studies.

Search strategy

Various terms for mild cognitive impairment, delirium and optical coherence tomography using the relevant Boolean operators and MeSH headings were used. Full details of the search strategy are included in the appendix.

There were no articles on OCT and delirium. The flow chart for OCT and POD is included in the appendix.

The rest of this chapter is therefore focused on OCT and MCI.

Study selection

A.N. and D.A. screened the search results and selected studies for inclusion in this review (figure 3.1). I.K.M resolved any areas of uncertainty.

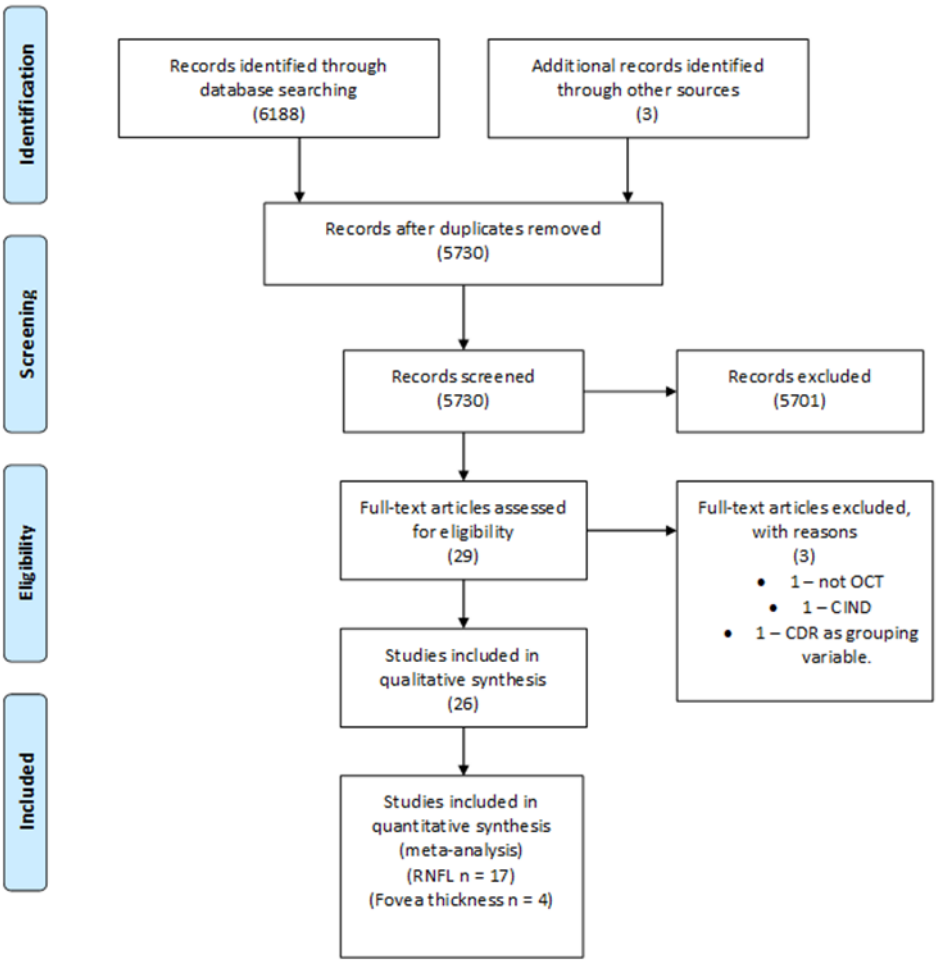

Figure 3.1: Study selection flow diagram – Optical coherence tomography and MCI

CDR = Clinical dementia rating scale

CIND = Cognitive impairment no dementia

Data collection

Two researchers (A.N. and D.A.) collected the data items for the review using a piloted form.

Data Items

The broad categories of data items collected were article information, study information, MCI assessment, and OCT.

Details of the data items collected are in the appendix.

Risk of bias in individual studies

Two assessors (A.N. and D.A.) tailored the quality assessment for diagnostic accuracy studies (QUADAS)-2 tool to assess the risk of bias (RoB) of included studies. There were four domains of RoB assessment i.e. patient selection, index test, target condition and reference standard, and flow and timing. The modified tool is included in the appendix. The assessors independently assessed the RoB of selected studies using the modified tool.

Human graders often validate software-driven retinal segmentation and measurement. This entails visual inspection of segmentation lines and adjustment as required. For this review, segmentation reported as software-driven only or validated by blinded human graders fulfilled blinding requirements.

Retinal images are centred on the optic disc (circumpapillary) or fovea centralis. To ensure comparability of the measurements across studies, for RNFL, only studies with circumpapillary measurements were included in the meta-analysis.

Summary measures

SMD (and 95% CI) of thickness of each retinal layer.

Risk of bias across studies

To mitigate potential bias due to different forms of OCT used (time-domain/spectral-domain), subgroup analyses (spectral-domain OCT) were performed.

The variety of tools used to diagnose MCI may also be a source of bias. To accommodate this, subgroup analyses (amnestic MCI) were performed.

Publication bias was assessed by visual inspection of a funnel plot for each analysis that included 10 or more articles[180].

Synthesis of results and additional analysis

For each retinal layer, a summary of methodology and outcomes is presented. For retinal layers with sufficient data, meta-analyses were also performed. Subgroup analysis of amnestic MCI and the relevant retinal layer was also carried out to accommodate bias resulting from the various subtypes of MCI. In addition, where there were sufficient data, subgroup analysis of spectral-domain OCT and the relevant cognitive impairment group was performed for the relevant layer.

Review Manager Version 5.3 (RevMan 5.3, The Cochrane Collaboration, 2014) and R Platform Version 3.5.2 (using Meta package, R foundation for statistical computing, Austria)

were used for the meta-analyses. SMD and 95% CI were assessed using random effects model. The measure of heterogeneity was Higgin's I^2.

Results

Database search identified 6188 articles. Three more articles were identified from article references. Of these, 26 articles fulfilled the review criteria (figure 3.1).

The number of studies for each retinal layer were

- Retinal nerve fibre layer – 21
- Ganglion cell-inner plexiform layer -9
- Macular thickness – 5
- Macular volume – 4
- Ganglion cell complex – 1
- Outer retinal layers – 1
- Choroid thickness – 1

Study Characteristics

Characteristics of included studies are in Table 3.1.

Author	**Year**	**Country**	**Type of study**	**No. of MCI**	**No. of controls**	**Mean age of MCI**	**Diagnostic criteria for MCI**	**OCT device**	**OCT type**	**Retinal layer measured**
Gao et al[215].	2015	China	Prospective	26	21	73.4 +/- 1.5	Petersen Criteria	Cirrus HD-OCT	Spectral domain	RNFL Macula Volume
Paquet et al[216].	2007	France	Prospective	23	15	78.7 +/- 6.2	MMSE based	Stratus OCT 3	Time domain	RNFL
Jiang et al[217].	2018	USA	Prospective	19	21	69.6 +/- 9.8	Albert Criteria	Zeiss Angioplex OCTA	Spectral domain	GC-IPL
Kwon et al[218].	2017	Korea	Prospective	30	30	72.2 +/- 5	Petersen Criteria	Cirrus HD-OCT	Spectral domain	RNFL Macular volume Macular thickness
Bulut et al[219].	2016	Turkey	Prospective	38	44	71.7 +/- 7.4	MMSE based	Cirrus HD-OCT	Spectral domain	Choroid thickness Macular thickness
Lad et al[220].	2018	USA	Prospective	15	18	73.1 +/- 9.1	Albert Criteria	Spectralis OCT	Spectral domain	RNFL GC-IPL

Querques et al[221].	2019	Italy	Prospective	12	32	76.3 +/- 6.9	Albert Criteria	Spectralis HRA OCT	Spectral domain	RNFL GC IPL (GCL + IPL) GCC Macular Thickness
Jiang et al[222].	2018	USA	Prospective	20	21	69 +/- 8.2	Albert Criteria	Cirrus OCT	Spectral domain	GC-IPL
Gimenez Castejon et al[223].	2016	Spain	Retro.	33	25	68.7 +/- 8	DSM-IV	Cirrus HD-OCT	Spectral domain	Macular Thickness
Ferrari et al[224].	2017	Italy	Prospective	29	49	70.5 +/- 5.5	Albert Criteria	Spectralis OCT	Spectral domain	RNFL GC-IPL
Uchida et al[225].	2018	USA	Prospective	22	36	68.9 +/- 6.8	Albert criteria	Cirrus HD-OCT	Spectral domain	Outer retinal layers
Wu et al[226].	2018	China	Prospective	24	30	72.3 +/- 9.1	Petersen Criteria	RTVue	Spectral domain	RNFL mGCC
Zhang et al[227].	2017	China	Prospective	49	49	70.9 +/- 6.1	Petersen Criteria	Stratus 3000 OCT	Time domain	RNFL
Ascaso et al[228].	2014	Spain	Prospective	21	41	Not separately reported	Winblad Criteria	Stratus OCT 3	Time domain	RNFL Macular Thickness Macular Volume
Feke et al[229].	2016	USA	Prospective	21	21	74.4 +/- 10.5	Winblad Criteria	Stratus OCT 3000	Time domain	RNFL
Cheung et al[132].	2014	Singapore	Prospective	41	123	70.4 +/- 10.2	Petersen Criteria	Cirrus HD-OCT	Spectral Domain	RNFL GC-IPL
Kasl et al[230].	2016	Czech Republic	Prospective	10	26	72 +/- 8	Petersen Criteria	Cirrus OCT	Spectral domain	RNFL
Knoll et al[213].	2016	USA	Prospective	17	17	74	2 or more SD below normative NIA-ADC UDS Battery + ADLs	Spectralis HRA+OCT	Spectral domain	RNFL Macular Thickness Macular Volume
Zhu et al[231].	2014	China	Prospective	47	167	76.1 +/- 8.2	Petersen and DSM-IV Criteria	Spectralis HRA+OCT	Spectral domain	RNFL
Shen et al[232].	2014	China	Prospective	23	52	74.4 +/- 3.2	Petersen Criteria	Cirrus HD-OCT 4000	Spectral domain	RNFL

Pillai et al[233].	2016	USA	Prospective	20	34	68.2 +/- 6.7	Albert Criteria	Cirrus HD-OCT 5000	Spectral domain	RNFL GCL Macular volume
Kesler et al[234].	2011	Israel	Prospective	24	24	71.0 +/- 10.0	Petersen Criteria	Stratus OCT 3	Time domain	RNFL
Oktem et al[235].	2015	Turkey	Prospective	35	35	74.1 +/- 6.3	Petersen Criteria	Cirrus HD OCT 5000	Spectral domain	RNFL
Liu et al[236].	2015	China	Prospective	26	39	70.2 +/- 6.5	Petersen Criteria	Stratus OCT 3	Time domain	RNFL
Sanchez et al[237].	2018	Spain	Prospective	192	414	76.5 +/- 7.1	Petersen Criteria	3-D OCT Maestro	Spectral domain	RNFL
Shao et al[238].	2018	USA	Prospective	24	21	69 +/- 8	Albert Criteria	Custom Built UHR OCT device	Spectral domain	RNFL GC-IPL

Table 3.1: Characteristics of studies included in the OCT and MCI review

Risk of bias within studies

Studies selected were largely low or unclear risk of bias (Figure 3.2 and 3.3). The majority of the unclear assessments was perceived to be due under-reporting of some aspects e.g. interval between cognitive assessment and retinal imaging.

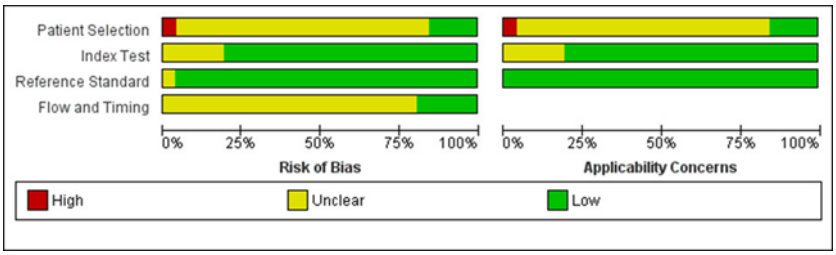

Figure 3.2: Risk of bias and applicability concerns graph of studies included in the OCT and MCI review.

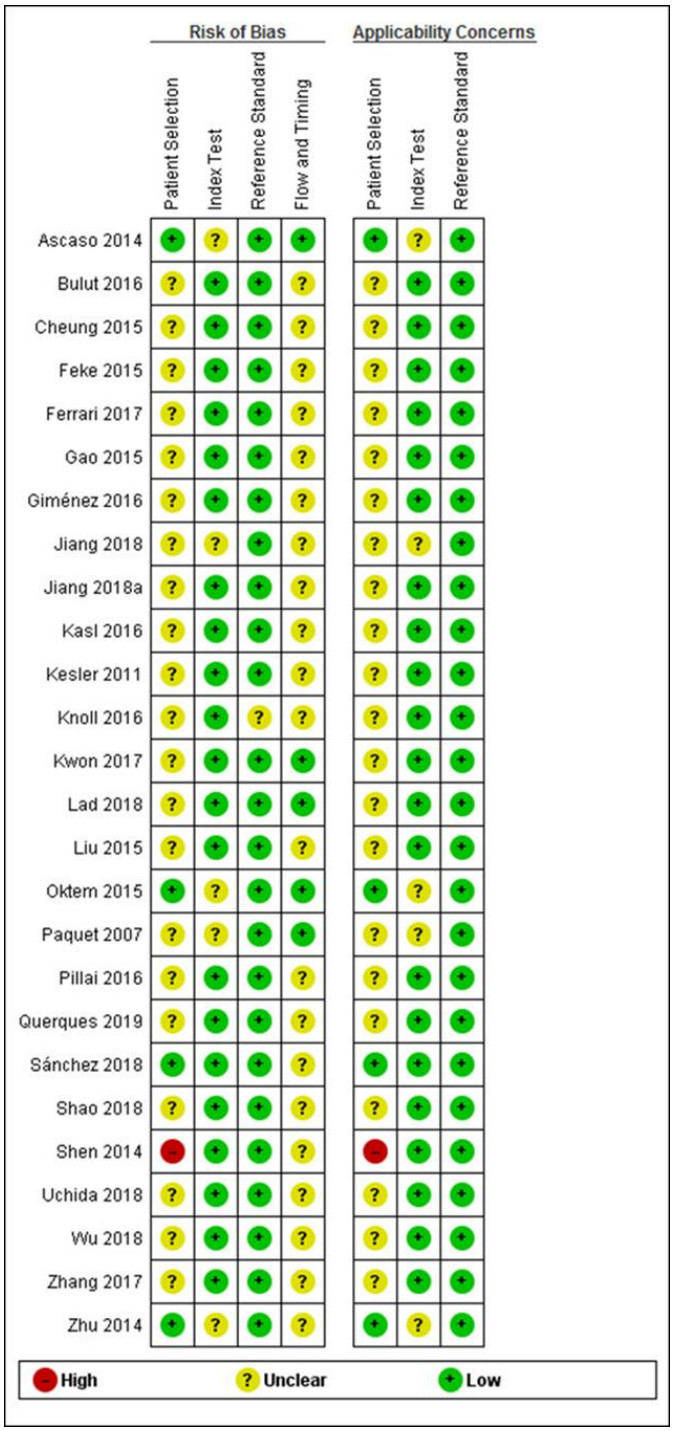

Figure 3.3: Risk of bias and applicability concerns summary of studies included in the OCT and MCI review

RNFL thickness and MCI

The thickness of the RNFL was compared between MCI and controls in 21 studies. Studies were prospective with a variety of sampling methods including consecutive recruitment,

cluster sampling, case-control and flyer distribution. The majority (15 studies) however did not specify the recruitment pattern.

Mild cognitive impairment - RNFL studies

Diagnostic criteria MCI –RNFL

The diagnostic criteria for MCI are depicted in figure 3.4.

Petersen criteria is retained for diagnosis according to the early version of Petersen's definition of MCI. In 2004, the international working group on mild cognitive impairment published an updated version of the Petersen criteria[239] [Ref Winblad 2004]. This update is referred to in this work as the Winblad criteria.

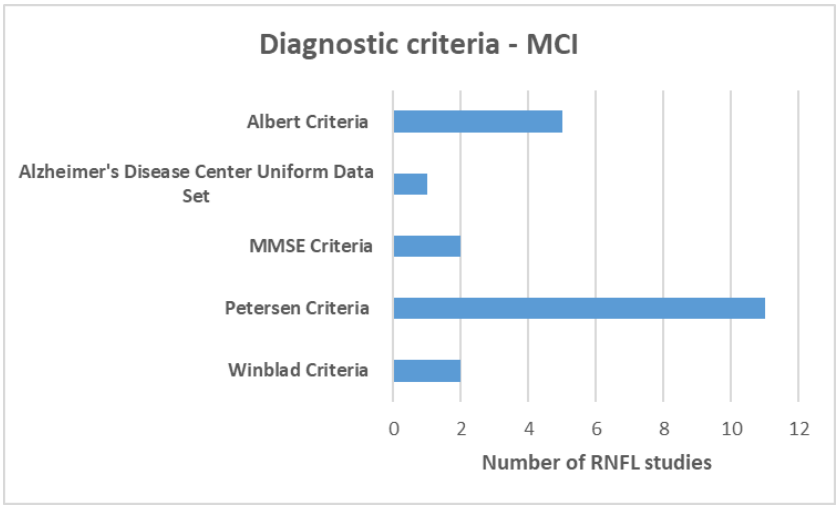

Figure 3.4: Diagnostic criteria for MCI in RNFL studies.

MMSE = Mini mental state examination

The intervals between cognitive screening and OCT were same day in six studies, within a year (unclear) in one and unstated in the remaining studies.

OCT - RNFL

Time-domain OCT was used in six studies and spectral domain in the remaining studies. Brands used are depicted in figure 3.5.

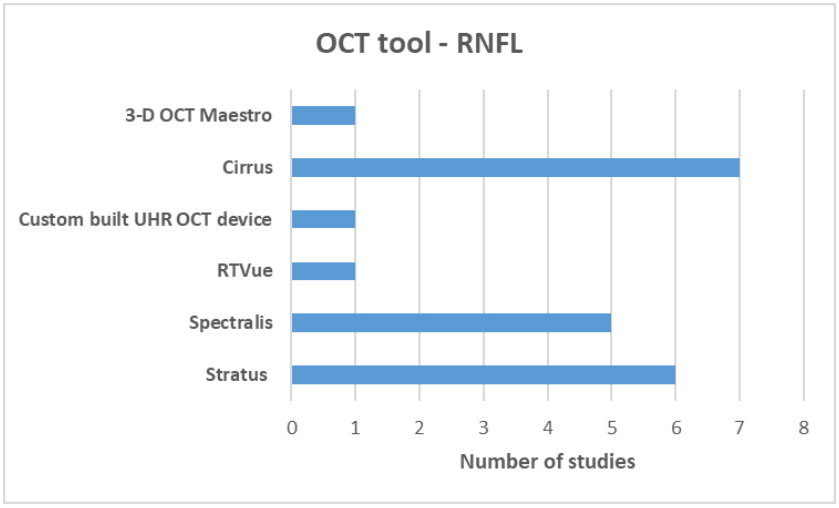

Figure 3.5: Brands of OCT device used in RNFL studies.

Eye(s) imaged for retinal measurements varied across studies.

Retinal measurements used were an average of both eyes in six studies, both eyes (paired for analysis) in three studies, both eyes (no correction for paired eyes) in two studies, best eye in two studies, one eye in five studies and unstated in three.

The retina was segmented by platform software (built into the OCT device) in 20 studies and non-platform software in one study.

Focus for retinal thickness measurement

RNFL was measured around the optic disc in 19 studies and fovea centralis in two studies. Subsequent analysis is on the 19studies that measured circumpapillary retinal nerve fibre layer thickness (cpRNFL).

Summary of findings - cpRNFL thickness and MCI

Nineteen studies explored the thickness of the cpRNFL in the context of MCI vs controls of which 15 also reported on quadrants within the cpRNFL. Eleven studies did not find a significant difference in the mean cpRNFL thickness between MCI and controls while eight studies reported the mean cpRNFL was significantly thinner in MCI when compared to controls.

With respect to specific quadrants, the differences between MCI and controls were inconsistent (table 3.2).

RNFL Quadrant	Significantly thinner in MCI	No Significant difference between MCI and controls	Other
Superior cpRNFL	4	10	1 – Superio-temporal
Temporal cpRNFL	3	11	1- Right eye only
Inferior cpRNFL	2	13	
Nasal cpRNFL	1	14	

Table 3.2: Findings of studies exploring thickness of cpRNFL quadrants in MCI vs Controls

Meta-analysis - cpRNFL thickness measured using any domain OCT in MCI vs controls

Seventeen studies had appropriate data for inclusion in a meta-analysis. There were 622 MCI cases and 1154 controls. In this analysis, cpRNFL was significantly thinner in MCI compared to controls (SMD -0.42, 95% CI -0.68 to -0.16, p = 0.002) (Figure 3.6). However, the I^2 was 82%.

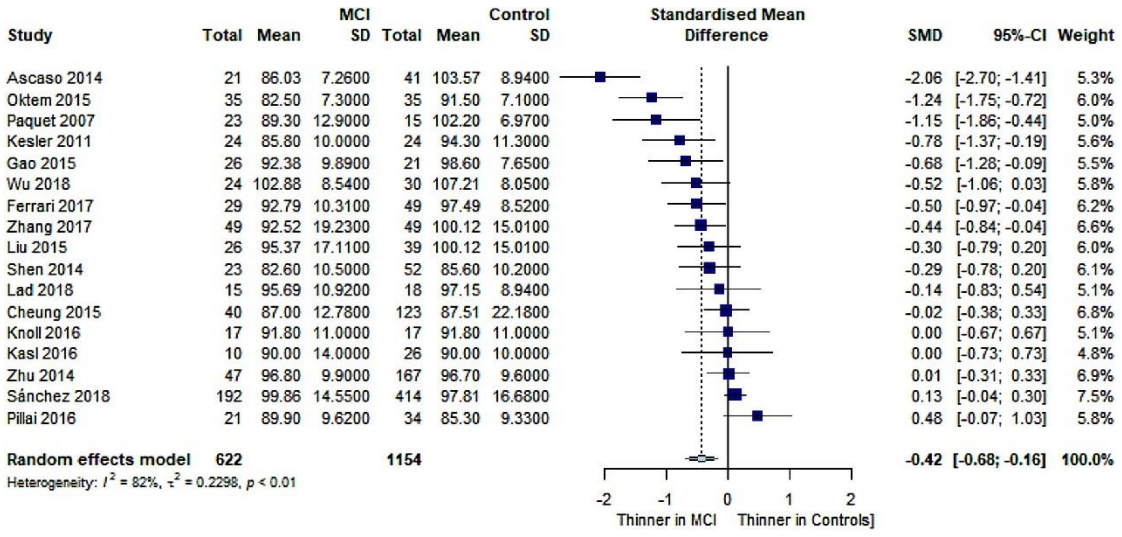

Figure 3.6: Forest plot of cpRNFL using any domain OCT device comparing MCI to controls.

To assess for publication and small study bias, a funnel plot was generated (Figure 3.7). Funnel plot symmetry was assessed using Egger's regression-based test. An intercept of 0.358 and p-value of 0.48 suggests low risk of publication bias.

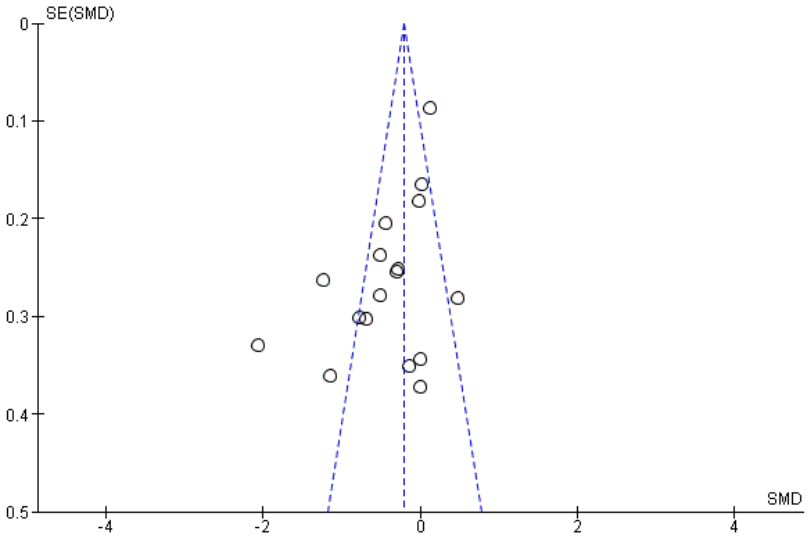

Figure 3.7: Funnel plot of studies included in the cpRNFL using any domain OCT and MCI meta-analysis.

Meta-analysis - cpRNFL thickness using spectral-domain OCT comparing MCI to controls

This subgroup analysis included 12 studies. There were 479 MCI cases and 986 controls. There was no significant difference in cpRNFL thickness between MCI and controls in this analysis (SMD -0.22, 95%CI -0.46 to 0.03, p = 0.08) (Figure 3.8). The I^2 of 72% suggests substantial heterogeneity.

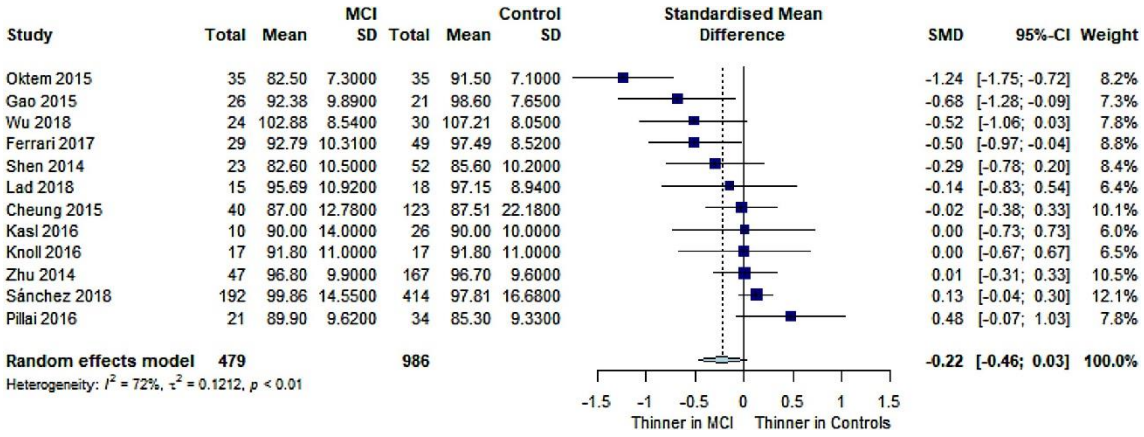

Figure 3.8: Forest plot of cpRNFL thickness using spectral domain OCT in MCI compared to controls.

Meta-analysis - cpRNFL thickness using any domain OCT comparing amnestic MCI to controls

In this subgroup analysis, we included only studies in which the MCI group was amnestic MCI as diagnosed using Petersen or Winblad criteria. This was an attempt to homogenise the MCI group. There were 13 studies, which included 540 amnestic MCI cases and 1036 controls.

The cpRNFL measured with any domain OCT was significantly thinner in amnestic MCI compared with controls (SMD -0.54, 95% CI -0.82 to -0.26, p = 0.0001) (Figure 3.9). Higgin's I^2 was 81%.

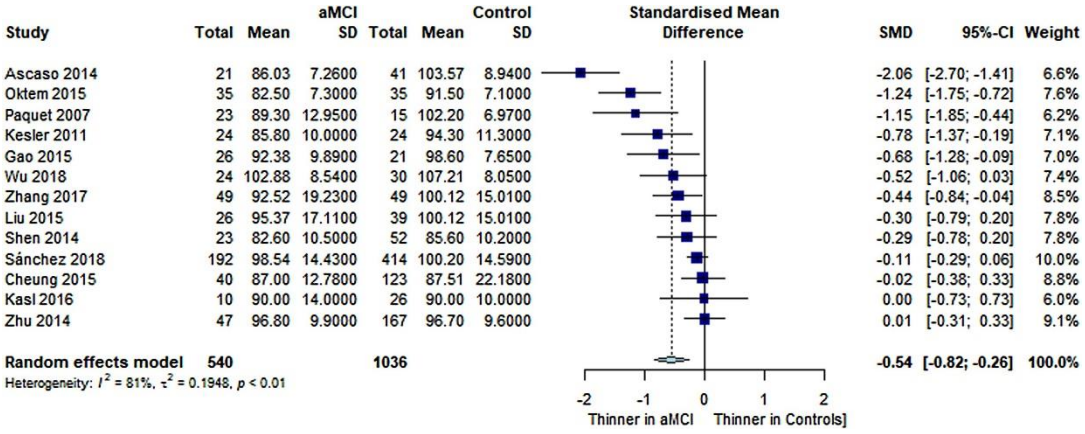

Figure 3.9: Forest plot of cpRNFL thickness using any domain OCT in amnestic MCI compared with controls.

Meta-analysis - cpRNFL thickness using spectral domain OCT comparing amnestic MCI to controls

There were eight studies, which included 397 MCI cases and 868 controls, in this subgroup analysis.

In this analysis, cpRNFL as measured using spectral domain OCT was thinner in amnestic MCI compared to controls (SMD -0.32, 95% CI -0.58 to -0.06, p = 0.02) (figure 3.10). The I^2 of 70% suggests substantial heterogeneity.

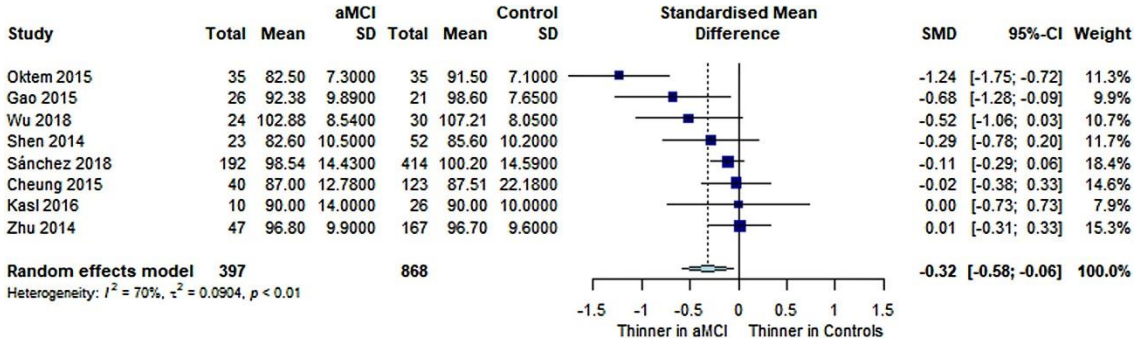

Figure 3.10: Forest plot of cpRNFL thickness using spectral domain OCT in amnestic MCI compared to controls.

Ganglion cell inner plexiform (GCIP) layer thickness and MCI

Nine prospective studies explored the difference in GCIP between MCI and controls. Sampling methods were unstated in seven studies.

Mild cognitive impairment - GCIP

The diagnostic criteria used for MCI are depicted in Figure 3.11.

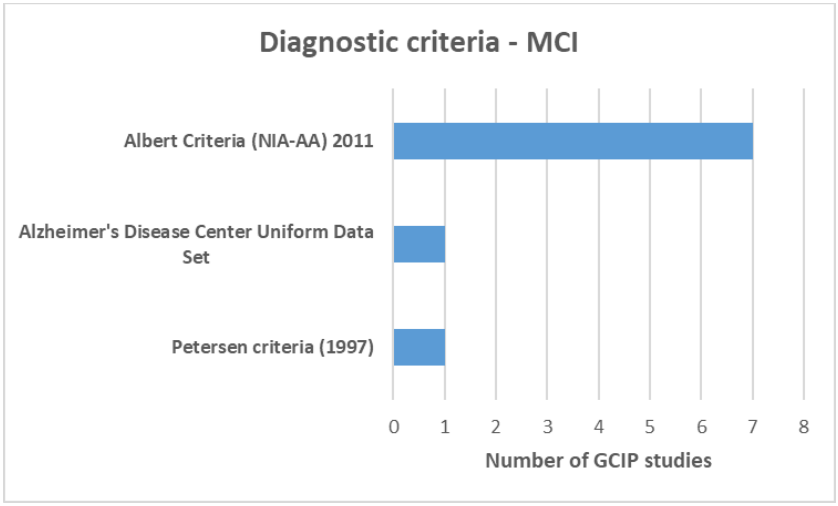

Figure 3.11: Diagnostic criteria for mild cognitive impairment in GCIP studies.

NIA-AA = National institute of aging and Alzheimer's association

The intervals between cognitive assessment and retinal imaging were same day in one study, within a year (unclear) in another and unstated in the remaining studies.

OCT - GCIP

Spectral domain devices were used in all the GCIP studies. Device brands used are depicted in figure 3.12.

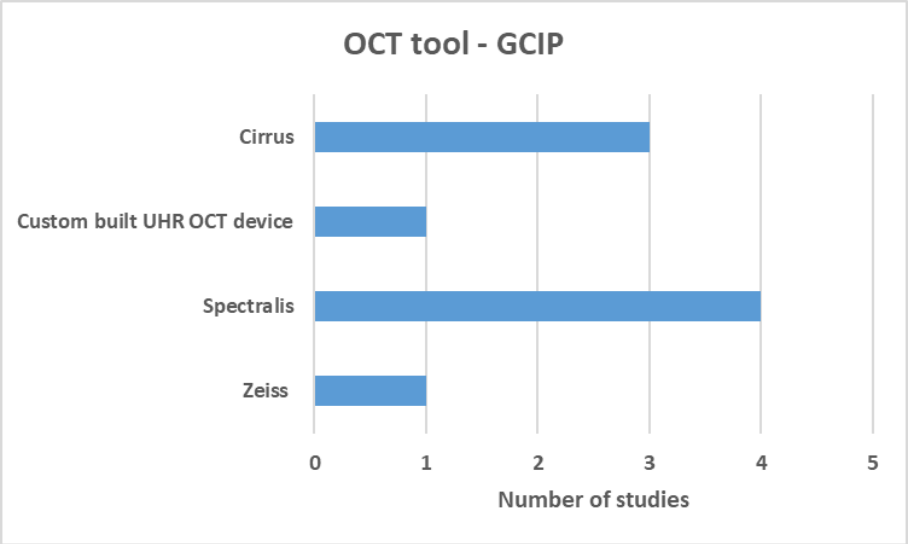

Figure 3.12: Brands of OCT device used in GCIP studies

Retinal measurement analysis used average of both eyes in one study, both eyes (paired) in two studies, one eye in five studies and unstated in one study. Retinal images were centred on the fovea in eight studies and optic disc in one.

The retina was segmented by platform software in five studies and non-platform software in the remaining studies.

Summary of findings - GCIP layer thickness in MCI compared to controls

Six studies did not find a significant difference in the average thickness of GCIP between MCI and controls. The study that measured GCIP thickness centred on the optic disc is included in these six studies. The average thickness of the GCIP layer was significantly thinner in MCI compared to controls in three studies.

Three studies reported GCIP layer quadrant or sectorial differences between MCI and controls. These were superior quadrant in one study, superior quadrant and inferonasal sector in another, and inferior quadrant, superonasal and inferotemporal sectors in the final study.

Meta-analysis - GCIP layer thickness in MCI compared to controls

The data available were not appropriate for a meta-analysis. Reasons are listed below.

- GCIP layer measurement centred on the optic disc – 1 study
- GCIP layer thickness values not congruent with normative values – 1 study
- GCIP layer measurements not provide – 3 study
- GCIP layer measurements provide in four studies of which two studies used an elliptical annulus and two used a circular annulus.

Macular and foveal thicknesses in MCI

Macular thickness was compared between MCI and controls in five studies of which four also reported on foveal thickness. There were four prospective studies. Recruitment patterns were unstated in four and the last study recruited consecutively.

MCI - macular thickness studies

Each study used a different diagnostic criterion for MCI. Criteria were Petersen criteria, Winblad criteria, Albert criteria, memory complaints and abnormal score on delayed memory recall tests, and DSM-IV criteria.

MCI subtypes also varies across studies. These included amnestic MCI in three studies, amnestic MCI without reference to activities of daily living in one study, and MCI due to AD in the remaining study.

Interval between cognitive assessment and retinal imaging was same day in two studies and unstated in the remaining studies.

OCT - macular thickness studies.

Four of the studies used spectral domain OCT.

Brands of OCT device were Cirrus in three studies, Spectralis and Stratus.

Both eyes (paired for analysis) were used in one study, average of both eyes in another study, both eyes (no correction for paired eyes) in another and one eye in the remaining two studies.

Images were centred on the fovea and segmentation was via platform software in all studies.

Summary of findings - macular and foveal thickness in MCI compared to controls

The macular thickness was not significantly different between MCI and controls in three studies. One study found the macular was significantly thinner in MCI and another study found the inner ring of the macular was significantly thicker in MCI.

One study found increased foveal thickness in MCI.

Meta-analysis - foveal thickness in MCI compared to controls

Only one study presented macular thickness data for MCI and controls therefore a meta-analysis was not performed.

Four studies on foveal thickness had sufficient data to support a meta-analysis. This analysis included 101 MCI cases and 147 controls.

There was no significant difference in foveal thickness between MCI and controls (SMD 0.05, 95% CI -0.54 to 0.63, p = 0.88) (Figure 3.13). The I^2 was 79%.

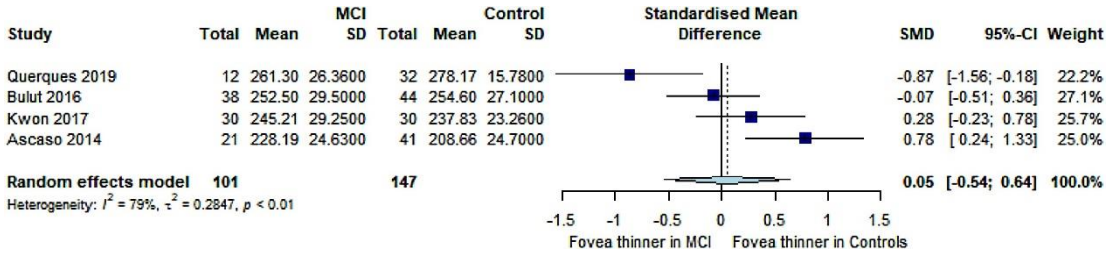

Figure 3.13: Forest plot of mean foveal thickness in MCI compared to controls

Macular volume in MCI

Macular volume was compared between MCI and controls in four, prospective studies. Recruitment patterns were unstated in two studies, consecutive in one study and frequency matching in one study.

MCI - macular volume

Each study used a different diagnostic criterion for MCI i.e. Petersen criteria, Winblad criteria, NIA-ADC UDS battery and Albert criteria. Despite the variety of criteria, three studies were on amnestic MCI and one study on MCI due to AD – Intermediate likelihood.

The interval between cognitive assessment and retinal imaging was unstated in two studies. In the other two, the intervals were same day and within a year.

OCT - macular volume

Three studies used spectral domain devices. Brands of OCT included Cirrus in two studies, Spectralis in one study and Stratus in one study.

Two studies used the average of both eyes and two used both eyes (paired for analysis).

Segmentation and volume estimates were via platform software in all studies.

Summary of findings - macular volume in MCI compared to controls

The macular volume was not significantly different in MCI compared to controls in two studies. Macular volume was higher in MCI in one study and lower in MCI in the fourth study.

There was insufficient data to support a meta-analysis.

Rarely researched retinal layers and MCI

Our search identified solitary studies on the choroid thickness, macular ganglion cell complex and outer retinal layer. The paucity of information precludes further analysis.

Discussion of OCT in MCI

Thinner cpRNFL was associated with MCI compared to controls in our main cpRNFL analysis (all devices and all MCI) and subgroup analyses of amnestic MCI (all OCT devices and only spectral domain OCT). Interestingly subgroup analysis of spectral domain OCT and MCI (all sub-categories) did not achieve statistical significance.

There was no significant difference in the thickness or volume (where applicable) of other retinal layers between MCI and controls. This may be a true finding or erroneous in view of the limited number of studies. In these other retinal layers, there was insufficient data to perform subgroup analysis on amnestic MCI.

The finding that thinner cpRNFL is associated with, particularly, amnestic MCI supports the premise that clinical features associated with established neurodegeneration, e.g. AD, may occur to a lesser extent in earlier stages of neurodegeneration e.g. amnestic MCI. The importance of screening for and excluding other local retinal and/or systemic pathologies that may cause thinning of the cpRNFL, cannot be over-emphasised.

Furthermore, a longitudinal MRI study found that patients with MCI that progressed to dementia had widespread microstructural white matter abnormalities at baseline compared to those who did not progress to dementia[240]. White matter tract abnormalities in amnestic MCI were found in locations unrelated to concurrent gray matter atrophy[241]. This may be significant to our finding of thinner cpRNFL but not in the GCIP layer. Other authors have

found a correlation between mean cpRNFL thickness and global brain, temporal lobe, and hippocampal volumes in early AD[242].

In this review, the variety of criteria used to diagnose MCI was problematic. The subgroup analysis of amnestic MCI was an attempt to homogenise the MCI group. Despite this, the heterogeneity as estimated by Higgin's I^2 remained high. Whilst study design related factors might have contributed to this heterogeneity, the variable conversion to dementia suggests that amnestic MCI may be a heterogeneous group[243, 244].

This review combined studies using different brands of OCT device and segmentation software. The absolute value of the cpRNFL may be different when measured using a variety of OCT devices[245, 246], however they were correlated[245, 247]. Deeper exploration suggests the differences may be due to nuances of the segmentation algorithms[248, 249] and differences in image resolution. However, the ability to differentiate between pathological thinning and controls is consistent[250]. That said, this author agrees with other authors and suggests that within one study the same brand (preferably the same device) is used in all participants at the same site[251, 252].

Unfortunately, we did not identify any studies on delirium/POD and retinal imaging.

With reference to our proposed trajectory of neurodegeneration, thinning of the cpRNFL measured using OCT may reflect advanced neurodegeneration (AD) and an earlier stage (MCI).

The development of POD in overtly cognitively intact older people is multifactorial. Intrinsic brain vulnerability is one such risk factor. Given the findings of this review, an exploration of cpRNFL thickness and the incidence of POD in cognitively intact older surgical patients is valid.

Conclusion

There is an association between thinning of cpRNFL and amnestic MCI. The association between preclinical neurodegeneration and cpRNFL awaits exploration. There are no studies on OCT and delirium/POD.

Intrinsic brain vulnerability – Retinal nerve fibre layer thickness chapter

Feasibility of retinal imaging using a hand-held OCT device and RNFL thickness in older people with and without POD recovering from hip fracture surgery.

Background

Our systematic review and meta-analysis demonstrated an association between thinning of the circumpapillary retinal nerve fibre layer (cpRNFL) and mild cognitive impairment (MCI), particularly amnestic MCI[202].

There is ample evidence that concurrent overt intrinsic brain vulnerability (e.g. AD or MCI) is associated with increased risk of postoperative delirium[15, 253].

Whilst the clinical features of neurodegeneration that occur in AD and MCI are apparent, some older people presenting for surgery may have neurodegeneration without overt clinical manifestations. This notion finds support in magnetic resonance imaging (MRI) and positron electron tomography (PET) studies, which demonstrate that structural changes in the brain may predate the clinical features of Alzheimer's dementia by a period up to a decade[82, 83]. This preclinical neurodegeneration may contribute to the risk of POD in affected people.

This work **does not** suggest that **all** older people who develop POD have covert neurodegeneration. Rather, given the high incidence of subsequent cognitive impairment/dementia associated with POD[254], there are two possible explanations. The first is that POD causes dementia. Although a few studies have demonstrated an association, there is little evidence of causality[96, 253]. The second explanation may be that some overtly cognitively intact older people, who develop POD, have covert neurodegeneration as a risk factor. The cytokine-surge associated with surgery and other perioperative stressors may serve to unmask this intrinsic brain vulnerability, presenting as POD. This covert neurodegeneration then progresses in the months and years after surgery to overt cognitive impairment. This premise is supported by the findings of a recent neuroimaging study[93]. In older surgical patients without dementia, there was an association between cortical thinning, in areas where thinning is associated with AD, and severity of POD.

Preoperative neuroimaging to detect preclinical neurodegeneration is expensive and not readily translatable to routine clinical use. Identifying readily measurable clinical features that may be associated with preclinical neurodegeneration, i.e. biomarkers of covert neurodegeneration, is long overdue. Such biomarkers may provide increased opportunity to study the role of preclinical neurodegeneration in the aetiology of POD in overtly cognitively intact older people.

Thinning of the cpRNFL is associated neurodegenerative disorders such as AD, Parkinson's disease[133, 203, 204] and MCI, particularly amnestic MCI[202]. Given that neurodegenerative changes in the brain predate symptoms by up to two decades, the notion that thinning of the cpRNFL may be present in preclinical neurodegeneration is plausible. If intrinsic brain

vulnerability is a risk factor for POD in **some** overtly cognitively intact older people, cpRNFL thinning may be associated with increased incidence of POD. The caveat is an absence of local eye disease e.g. glaucoma or systemic disease e.g. diabetes that are associated with thinning of the cpRNFL.

Optical coherence tomography (OCT) is used to acquire images of the eye. The technology is non-invasive and uses low-coherence interferometry to visualise retinal layers at near-microscopic level, permitting measurement of various retinal layers. In addition to retinal thickness measurement, OCT is widely used by opticians and ophthalmologists to diagnose and monitor ocular diseases such as glaucoma and diabetic retinopathy[255, 256]. It has also gained a foothold in clinical research in other specialities e.g. neurology.

Standard OCT is a bulky, tabletop device, which is not readily portable. Obtaining retinal images requires a cooperative person, positioned sitting upright, with supports for the chin and forehead. Hip fracture is the commonest indication for emergency surgery in older people and associated with a significant incidence of POD[257]. Obtaining retinal images with the tabletop OCT device in this cohort may be challenging.

Recently, hand-held OCT (HH-OCT) has become available (Figure 4.1). HH-OCT is used in research and to aid clinical diagnoses in newborn and young children[258].

In this study, we assess the feasibility of bedside retinal imaging with HH- OCT in older hip fracture surgery patients, seek preliminary evidence for/against cpRNFL thickness as a biomarker of POD and assess utility, if feasibility is demonstrated.

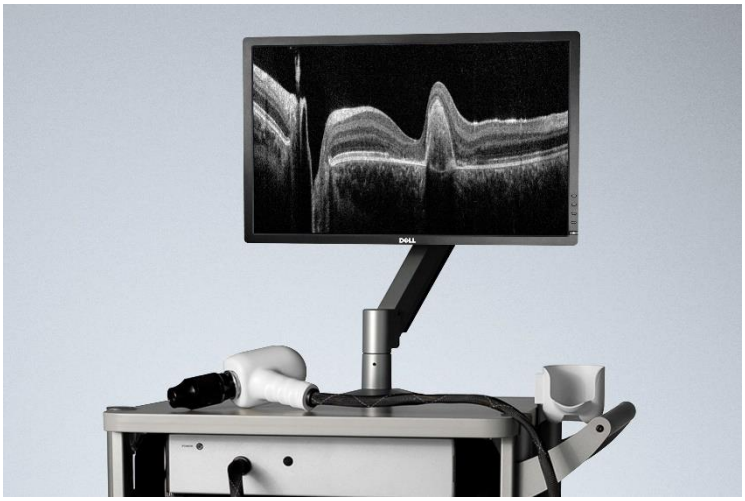

Figure 4.1: Handheld OCT device

Objectives

Primary objective

Assessment of the feasibility of acquiring retinal images using a HH-OCT at the patient's bedside in older people recovering from hip fracture surgery.

Secondary objectives

Exploratory: Compare cpRNFL thickness in people who have recovered from postoperative delirium to those who did not experience postoperative delirium.

Utility: Assess the proportion of our hip fracture population (during the study period) in whom there were exclusions due to retinal or other diseases known to affect the cpRNFL thickness. This is to determine utility.

Methods

Study design

A prospective, observational, feasibility study involving people aged ≥ 65 years old recovering from primary hip fracture surgery in a secondary care centre.

The protocol was registered with Clinicaltrials.gov (NCT04041336) and NHS HRA REC (reference 19/NW/0192) approved the study protocol.

This report is structured according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

Participants were recruited from the trauma wards of Queen's Medical Centre, Nottingham. Batches of consecutive recruitment were used to accommodate the logistics of equipment availability and the challenges of the COVID-19 pandemic. The periods of recruitment were Block 1: 30/08/2019 – 13/09/2019, Block 2: 03/02/2020 – 10/03/2020, Block 3: 08/08/2020 – 01/10/2020.

Participants

During each period of recruitment, patients recovering from hip fracture surgery were screened for inclusion in this study.

Inclusion criteria were

- age ≥ 65 years old
- recovering from primary, unilateral hip fracture surgery
- ability to comply with retinal imaging
- ability to give written informed consent

Exclusion criteria included

- preoperative diagnosis of cognitive impairment (e.g. dementia, mild cognitive impairment and prevalent delirium)
- abbreviated mental test score (AMT) on admission ≤ 7)
- significant eye pathology (e.g. glaucoma, severe myopia, diabetic retinopathy, retinal surgery, dense cataracts, age-related macular degeneration, eye trauma)
- postural or movement disorders precluding retinal imaging (e.g. severe tremor)
- intracranial pathology (head injury, previous cerebrovascular accidents or transient ischaemic attacks, multiple sclerosis, intracranial space occupying lesions, and neurodegenerative conditions such as Parkinson's disease)
- systemic malignancy
- deteriorating clinical condition
- multiple injuries
- severe frailty
- hip fracture sustained during hospital admission
- not expected to survive the perioperative period

Recruitment occurred during the first week after surgery, after postoperative day two. This was to allow recovery from the acute effects of the anaesthesia/surgical intervention (Figure 4.2).

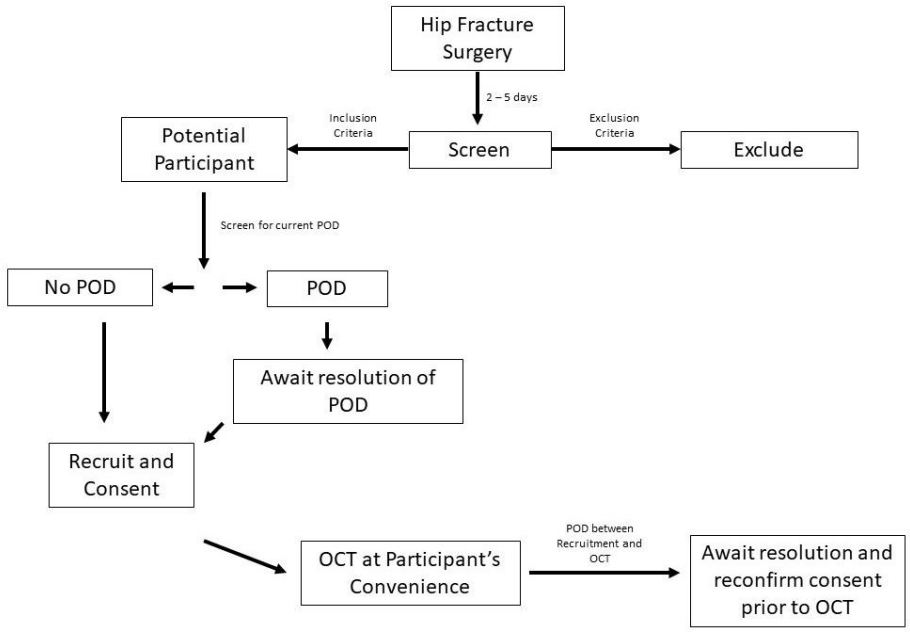

Figure 4.2: Flowchart of participant recruitment.

OCT image acquisition

We elected to acquire the retinal images after surgery. This was to reduce the burden on the participants, often in pain on admission and undergo interventions for pain

management and preparation for urgent surgery. The cpRNFL thickness is stable in the short term, with an estimated age-related thinning of approximately 0.52µm/year[137]. This permitted the use of HH-OCT, in this study, after surgery and, where relevant, after an episode of POD had resolved.

Timing of OCT was dependent on participant convenience, ongoing clinical needs and occurrence of POD. In the event of current POD, retinal imaging was deferred until after resolution.

The retinal images were acquired using the HH-OCT device (Leica Microsystems, Envisu C2300, Wetzlar, Germany). Volumetric images were acquired using a 12 mm x 12 mm scan protocol (1000 A-scans x 100 B-scan).

The main operator (A.N.) of the device was fully trained by the manufacturer and demonstrated the ability to attain high quality images prior to the study. When available, a second device operator (J.S., technician) aided the main operator with image acquisition, i.e. acquired the images while A.N. focussed the light beam. A.N. and J.S. had practised image acquisition on volunteers prior to the study.

Participants were scanned at their bedside in the sitting or recumbent position. This was determined by participant convenience and preference. The right eye was the default eye for imaging and the left eye used if right eye images were suboptimal or not possible. Mydriatic agents were not used.

Duration of image acquisition was documented, as were the number of repeats required to achieve a usable image. The images were segmented and analysed by A.N. and findings reviewed by two OCT experts (Z.T. (external supervisor)/F.P.).

Image analysis:

ImageJ (http://imagej.nih.gov/ij/; National Institute of Health, Bethesda, Maryland) was used to batch convert the HH-OCT images into a file format that could be analysed using Copernicus SR software (Optopol Technology, Zawierci, Poland)[258].

Automated retinal segmentation was inspected. Segmentation errors were manually corrected.

Measurement of the mean cpRNFL thickness was at a 2.83mm diameter ring centred on the optic disc to adjust for the conversion of the image window. The superior (S), nasal (N), inferior (I) and temporal (T) cpRNFL quadrant thicknesses were also measured. (Figures 4.3 and 4.4)

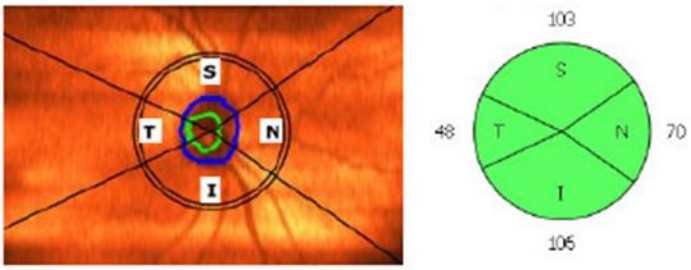

Figure 4.3: Fundus reconstruction depicting the area of analysis and thickness in a participant.

Numbers are the thickness in µm of the corresponding quadrant in this participant.

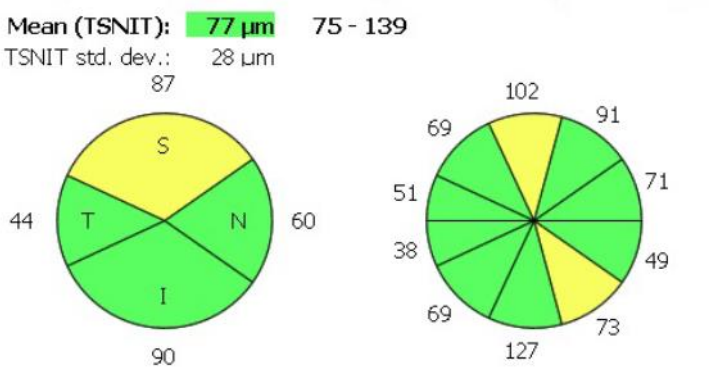

Figure 4.4: Circumpapillary retinal nerve fibre layer thickness in a participant.

The cpRNFL thickness divided into 10 radial segments (using the GDx Nerve Fiber Analyzer protocol, Carl Zeiss Meditec). The quadrants are created by amalgamating two (temporal), two (nasal), three (superior) and three (inferior) radial segments. The colours represent comparison to age-adjusted normative values (green = normal, yellow = borderline and red = out of range). The numbers around the circles are the thicknesses in µm of the relevant quadrant or segment in a study participant.

Standard care

All participants were cared for on an acute trauma ward, which operates a shared orthogeriatric care model, in line with national guidance. Surgery, anaesthesia and perioperative care follow national guidance, including senior surgical and anaesthetic care, prompt surgery, nerve block analgesia, formal assessment of delirium pre- and postoperatively and avoidance of deliriogenic drugs. In addition, nursing staff, at least twice daily, routinely conduct assessment for behavioural changes that may suggest POD.

Diagnosis of postoperative delirium

After recruitment, participants' nursing and medical records were reviewed for evidence of prior POD during the current admission. If OCT was not performed at recruitment, participants were assessed daily for POD using DSM IV criteria. This was in addition to the routine nursing assessments described above. The usual care team was informed if the researcher diagnosed POD and HH-OCT was postponed until POD resolved. At discharge, participants' nursing and medical records were searched for evidence of POD after HH-OCT.

Participants grouping was no POD and POD.

Outcomes

Feasibility

Primary feasibility: Success of acquisition of retinal images using HH-OCT, defined as obtaining at least one retinal image with measurable cpRNFL thickness.

Secondary Feasibility: Number of attempts, time to acquisition and number of device operators.

Exploratory outcome: cpRNFL thickness (mean and quadrants) in no POD and POD groups.

Utility outcome: Proportion of patients recovering from hip fracture surgery during the study period without concurrent diseases that affect the cpRNFL.

Sample size: A feasibility study hence a pragmatic sample size of 30 participants in line with guidance[259].

Statistical methods

Feasibility and group proportions reported using descriptive statistics. For analysis of cpRNFL thickness, the grouping variable was no POD vs POD. Association between mean/quadrant cpRNFL thicknesses and incidence of postoperative delirium assessed using the Mann-Whitney test. Statistical analysis was performed using IBM SPSS for windows vs 29 (SPSS Inc., IBM, USA) and R Platform version 3.5.2 using Meta package (R foundation for statistical computing, Vienna, Austria)

Results

There were 250 people of age ≥ 65 years recovering from primary hip fracture surgery at the research site of whom 61 fulfilled inclusion criteria. Of these, 21 patients declined, five were discharged prior to imaging, recruitment was halted by the COVID-19 pandemic in three, and two were transferred to another institution prior to scanning (Table 4.1). This resulted in 30 participants in this study (26 - no POD, 4 – POD) (Table 4.2). Although the average age of the POD group was higher than the no POD group, the difference was not statistically significant.

	Whole cohort (n= 250)	Passed screening (n = 61)	Included (n = 30)
Sex (female / male)	168/82	42/19	17/13
Age in years: median (IQR)	84 (78-89)	81 (73 – 85)	76 (70 – 81)
Experienced POD	Not assessed	Not assessed	4

Table 4.1: Recruitment pattern and demographics of participants and excluded people.

	No POD	POD	p-value
Female/Male	14/12	3/1	0.427
Age in years +/- SD	76 +/- 8	81+/- 4	0.2
AMTS score on admission(n)	8(1) 9(5) 10(20)	8(1) 9(1) 10(2)	0.256
CCI grade (n)	Mild (2) Moderate (13) Severe (11)	Mild (0) Moderate (2) Severe (2)	0.837

Table 4.2: Baseline characteristics of participants

AMTS = Abbreviated mental test score, POD = postoperative delirium

CCI = Charlson Comorbidity Index

CCI Grade = Mild (CCI Score 0 – 2), Moderate (CCI score 3 – 4), Severe (CCI score ≥ 5)

Feasibility

Primary feasibility

Of 30 participants in this study, retinal images from which all segments of cpRNFL thickness could be analysed were obtained in 25 participants (83%). An additional participant had clear images, but the inferior part of the measurement area was obscured. This final participant's data were included in analysis of retinal segments with available data. The retinal images were too dark to segment in four participants and thus excluded from the exploratory analysis.

Secondary Feasibility

Participants' positions during scanning were lying in bed - 23 (76.7%) participants, sitting on a chair - 6 (20%) participants and sitting on edge of bed – 1 (3.3%) participant.

Based on availability, there were two scanner operators for 21 participants and one for the remaining nine participants. The four participants excluded from the exploratory analysis due to dark images had two scanner operators.

While the default eye was the right eye, the image used for analysis was the left eye in four participants (unclear right eye images x 2, right eye surgery and right eye dense cataract).

The number of attempts (median (IQR)) to achieve a scan for analysis was 2 (2 – 4).

Time to achieve scan for analysis was available in 24 of 25 participants with fully analysable scans. The median (IQR) time was 3 (2 – 4.25) minutes.

Exploratory outcome

Circumpapillary retinal nerve fibre layer thickness (cpRNFL) measurements

Mean and inferior cpRNFL was measured in 25 participants of whom four had postoperative delirium. Superior, nasal and temporal segment data was available in 26 participants. Measurement was at a circumpapillary ring with an inner ring diameter of 2.83mm and a ring thickness of 0.10mm

The findings are in Table 4.3, and Figures 4.5 & 4.6.

	No POD (n = 22) *	POD (n = 4)	Mann-Whitney U statistic	p-value (exact)

Mean cpRNFL µm	91 (83 – 94.50)	75.50 (68.75 – 85.25)	9.0	0.011
Superior cpRNFL µm	102 (99 – 105.50)	84 (77.75 – 94.75)	7.0	0.005
Nasal cpRNFL µm	67 (57 -76)	59 (48 – 61.75)	23.0	0.150
Inferior cpRNFL µm	106 (88 – 117.50)	91.5 (79.50 – 104.25)	25.0	0.231
Temporal cpRNFL µm	54 (49.50 -58)	46.5 (40 – 52.25)	14.0	0.032

Table 4.3: Exploratory analysis of mean and segmental circumpapillary retinal nerve fibre thickness between participants who did not have postoperative delirium and those who had postoperative delirium

Summary statistics - median (IQR)

*N = 22 except mean cpRNFL and inferior cpRNFL where n = 21

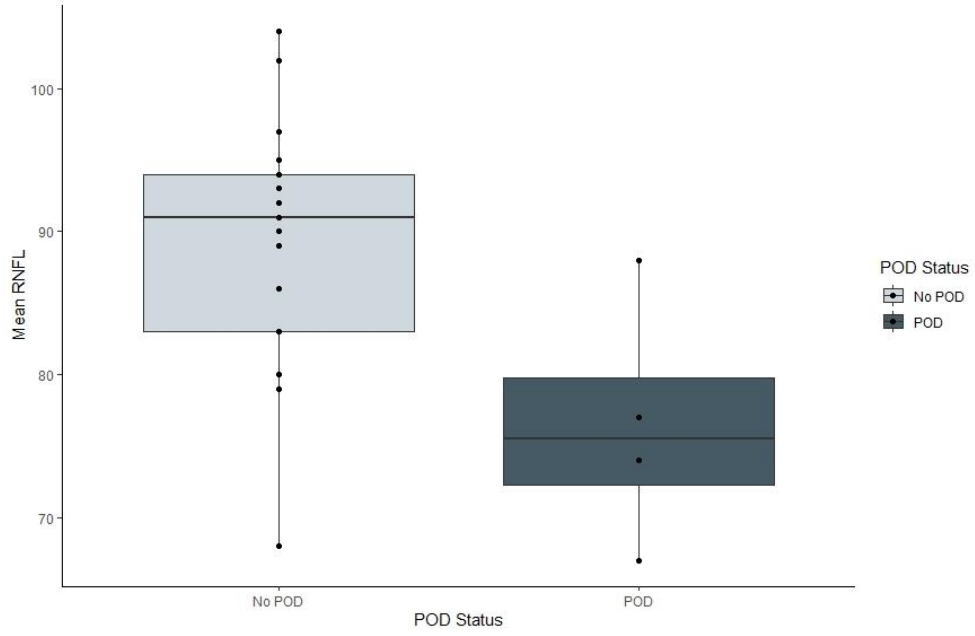

Figure 4.5: Box plot of Mean cpRNFL (µm) at Ring diameter 2.83mm in participants who did not have postoperative delirium and participants who had postoperative delirium. Individual participant's values indicated by dots.

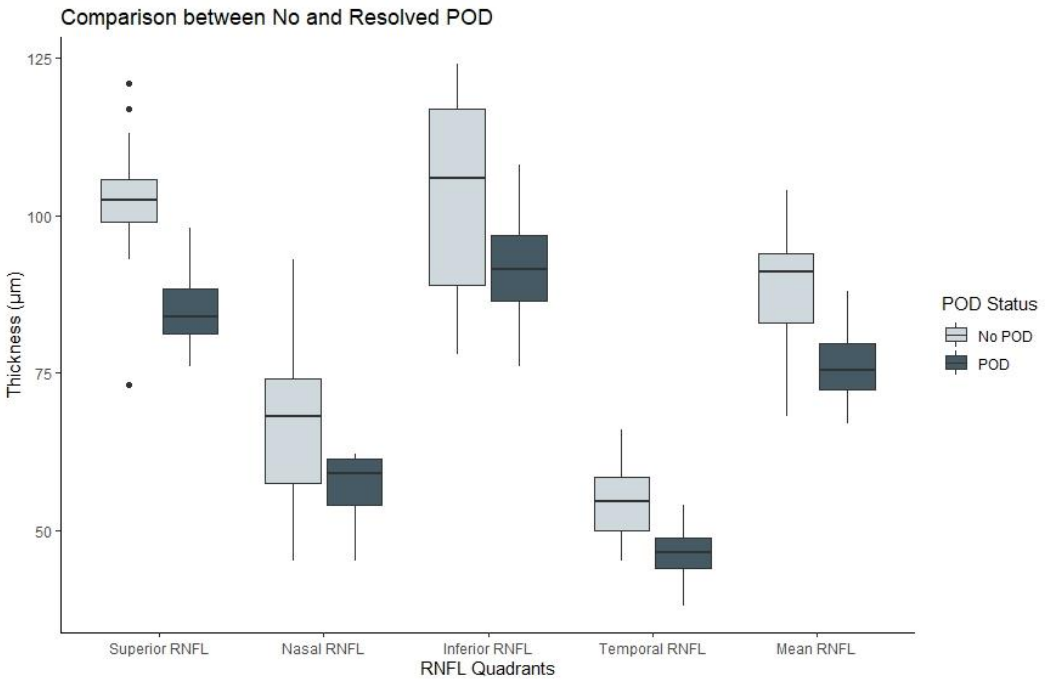

Figure 4.6: Boxplot of cpRNFL thickness (µm) by quadrants at ring diameter 2.83mm comparing participants who had postoperative delirium to those who did not experience postoperative delirium.

Utility outcome

Of 250 people recovering from primary hip fracture surgery during the study period, 189 had comorbidities that precluded participation in this study. Although the majority of excluded patients had multiple exclusion criteria we report here on the most significant exclusion criterion for each participant. The primary reason for exclusion are outlined in Table 4.4.

Primary reason for exclusion	Number
Inability to give informed consent (dementia, cognitive impairment or prevalent delirium)	89
Local eye pathology (blind, glaucoma, macular degeneration, retinal surgery or severe cataracts)	21

Systemic/neurodegenerative disease with known associations with retinal pathology (Diabetes, Parkinson's disease)	20
Brain pathology (head injury, tumours, CVA, recurrent TIA)	21
Acute clinical status (current cancer, clinical deterioration)	29
Inability to comply (frailty, multiple injuries, severe tremor)	5
Hip fracture sustained during hospital admission	4

Table 4.4: Reasons for exclusion

CVA = Cardiovascular Accident, TIA = transient Ischaemic Attack

One hundred and twenty-nine patients had local, neurodegenerative or systemic conditions that may independently affect the cpRNFL. 48.4% of patients recovering from hip fracture surgery did not have modifiers of cpRNFL thickness.

Discussion

Acquisition of retinal images from which cpRNFL thickness can be measured, using a hand-held OCT device, by non-specialist operators, at the patients' bedside is feasible.

The exploratory analysis suggests that in a carefully selected cohort, the average cpRNFL thickness in participants who had postoperative delirium may be thinner than in participants who did not have postoperative delirium; however, the study was not powered for this outcome.

The superior and temporal cpRNFL quadrants were also significantly thinner in POD compared to no POD. This is interesting as our systematic review demonstrated these are the most frequently affected cpRNFL quadrants in MCI. The significance of this requires further exploration.

That said, approximately half the patients with primary hip fracture admitted to our institution during the study period had other potential causes of cpRNFL thinning.

The original plan for this study was to investigate the cpRNFL thickness in people recovering from hip fracture surgery using a tabletop OCT device. This would entail transferring participants to the local OCT device (in ophthalmology clinic). The logistic challenges this transfer and positioning posed resulted in our search for a portable option. The option of a

flexible boom arm was considered and dismissed. Whilst the boom arm addressed the concern about positioning, challenges of patient transfer to the OCT device location remained. Incidentally, in a small study on intensive care patients, the success rate of optic nerve head imaging, using a boom arm, was 76% despite the use of mydriatic agents[260]. Moreover, the ONH images were to identify gross pathologies such as optic disc swelling.

Further exploration identified the HH-OCT device, which was the only commercially available HH-OCT device (Envisu C, Leica Microsystems) suitable for our purposes. The ability of non-specialist researchers to acquire, accurately segment and measure cpRNFL thickness in 83% of our participants, using the HH-OCT device, is an important outcome. The ability to acquire retinal images, without mydriatics, at the bedside, opens a wide range of possibilities for future research.

Our hypothesis is that some, overtly cognitively intact older people have preclinical neurodegeneration. In these people, the covert neurodegeneration may increase the risk of developing postoperative delirium. From literature and our systematic review cpRNFL thinning is associated with AD and MCI. The finding of a potential association between thinning of the cpRNFL and POD suggests further exploration is justified. It must however be recognised that utility may be limited to those people who do not have comorbidities that influence cpRNFL.

This study is an early step to contribute to the understanding of the link between POD and subsequent cognitive impairment/dementia. It also is a starting point for clarifying the role of covert neurodegeneration in the aetiology of POD in older people, particularly the cohort of POD that subsequently develop cognitive impairment/dementia.

More precise risk stratification of POD in older people is an urgent problem given the associated adverse outcomes. While there are several POD prediction tools, the predictive capability of these tools is suboptimal[261, 262]. Overt features of neurodegeneration such as cognitive impairment and Folstein's mini mental state examination are included in some tools, but there is an absence of object measures of covert, preclinical neurodegeneration. This is not surprising given the expense of brain MRI/CT screening scans in cognitively intact older people scheduled for surgery. The development of an inexpensive bedside tool that could act as a surrogate for screening for preoperative covert neurodegeneration may further improve POD risk assessment.

With this study, we have taken a first step in exploring the potential of HH-OCT as a bedside tool that may be used to measure cpRNFL as a potential biomarker of intrinsic brain vulnerability in POD risk assessment.

That said, this study has some limitations. The HH-OCT device does not have an integrated automated retinal segmentation software mandating the use of non-platform software to perform the analysis. This limited the ability to predict the final image clarity, after transfer to non-platform segmentation software. In addition, cpRNFL measurement may be affected by the refractive index of the eye[136, 263]. Calibration of the device with each participant's refractive index, where applicable, is advised. Unfortunately, our glasses-wearing

participants did not have this information readily available. Finally, a limited number of participants (13%) developed POD in this study.

Conclusion

In conclusion, retinal imaging at the patient's bedside, using the hand-held OCT is feasible. Our data suggests that in the absence of comorbidities associated with alteration of the cpRNFL (e.g. eye disease), thinning of the cpRNFL may be associated with an increased risk of postoperative delirium. This needs to be confirmed in future prospective studies.

Intrinsic brain vulnerability – Electroencephalography chapter

Feasibility of raw occipital EEG acquisition using a depth of anaesthesia monitor and impact of posterior EEG power on POD in cognitively intact older people

Background

The search for potential biomarkers of intrinsic brain vulnerability highlighted some features of electroencephalography (EEG) as potential candidates. The EEG provides a temporal window into brain function and is particularly attractive because it may be acquired using non-invasive scalp electrodes. Please see information box 5.1 for relevant EEG nomenclature and definitions[264].

EEG basics

Frequency: Number of cycles per second (units - Hz)

Amplitude: Difference between the peak and trough of the wave (units- microvolts)

Power: Amplitude of the wave squared

Band: Portion of the EEG frequency spectrum

Power spectrum: Graphical display with frequency on the x-axis and power on the y-axis

Digital spectral array (DSA): Graphic representation with time on the x-axis, frequency on the y-axis and power represented with a colour spectrum.

Bands and frequencies

- Beta band: 14 – 30Hz
- Alpha band: 8 – 13Hz
- Theta band: 4 – 7Hz
- Delta band: 0.5 – 4Hz

Information box 5.1: EEG and processed EEG nomenclature

The EEG is the summation of excitatory and inhibitory postsynaptic potentials mainly from the pyramidal neurons in the superficial cortical layers[265]. This is particularly important because these pyramidal neurons receive the non-specific thalamocortical afferents. In the resting state with eyes closed, some degree of synchronisation of these thalamocortical afferents occurs resulting in a slower high amplitude dominant oscillation with a frequency in the alpha bandwidth i.e. 8 to 13Hz. This is the posterior dominant rhythm (PDR). In the eyes open state, the activity of these afferents is desynchronised resulting in a fast, low amplitude EEG wave with a frequency in the beta bandwidth i.e. 14 – 30 Hz. This desynchronization is believed to be due to the activation of the visual cortex with the eyes open and is largely driven by the reticular activating system. Although the EEG changes between eyes-open and eyes-closed are consistent across adults, physiologic aging is associated with lower amplitude of the occipital alpha wave. This was demonstrated in a study comparing the PDR in 107 older people to 108 young participants[146]. In that study the amplitude of the PDR was higher in the younger cohort. Incidentally, in addition to reduced power in the PDR, resting state physiological aging is associated with global slowing of the EEG[144]. Although global slowing is associated with physiological aging, this slowing is more pronounced in people with AD and, to a lesser extent, MCI[147-149].

Concerning the PDR, pathological aging is associated with more profound amplitude reduction when compared to physiologic aging[149]. In their study comparing the PDR in participants with MCI, dementia and age matched controls, Babiloni et al reported the trend in amplitude as normal old > MCI > AD. Crucially, the same research team, in a different study, demonstrated a correlation between the occipital gray matter density and the posterior dominant rhythm amplitude [150].

Considering our hypothesis that features associated with overt neurodegeneration, e.g. MCI and dementia, may be present to a lesser extent in overtly cognitively intact older people with covert neurodegeneration, the findings of the studies discussed are encouraging.

Thus, given the PDR may be affected by MCI and Alzheimer's disease, it is plausible that covert neurodegeneration may be associated with some anomalies of the PDR albeit to a lesser extent.

However, EEG acquisition traditionally involves a multi-electrode EEG device operated by a trained technician or neurophysiologist. Research to assess the prediction of POD by the power of the occipital EEG (eyes-open and eyes-closed) may be conducted using a traditional EEG device. However, if PDR emerges as a potential biomarker of intrinsic brain vulnerability, translation to routine clinical application may be curtailed by the financial and time burden associated with traditional EEG acquisition.

Fortuitously, processed EEG (pEEG) monitoring is routine used during general anaesthesia to guide the depth of anaesthesia and anaesthetic dose titration.

The pEEG device acquires raw EEG via adhesive electrodes that are quick to apply. Frontal, single channel monitoring is the norm although some devices can support two-channel monitoring, usual bilateral frontal monitoring. Processing of the raw EEG, via proprietary algorithms, yields a displayed depth of anaesthesia index number[266, 267]. Modern devices

also display a power spectrum, digital spectral array, the raw EEG and the ability to display two channels of EEG simultaneously, where applicable (Figure 5.1).

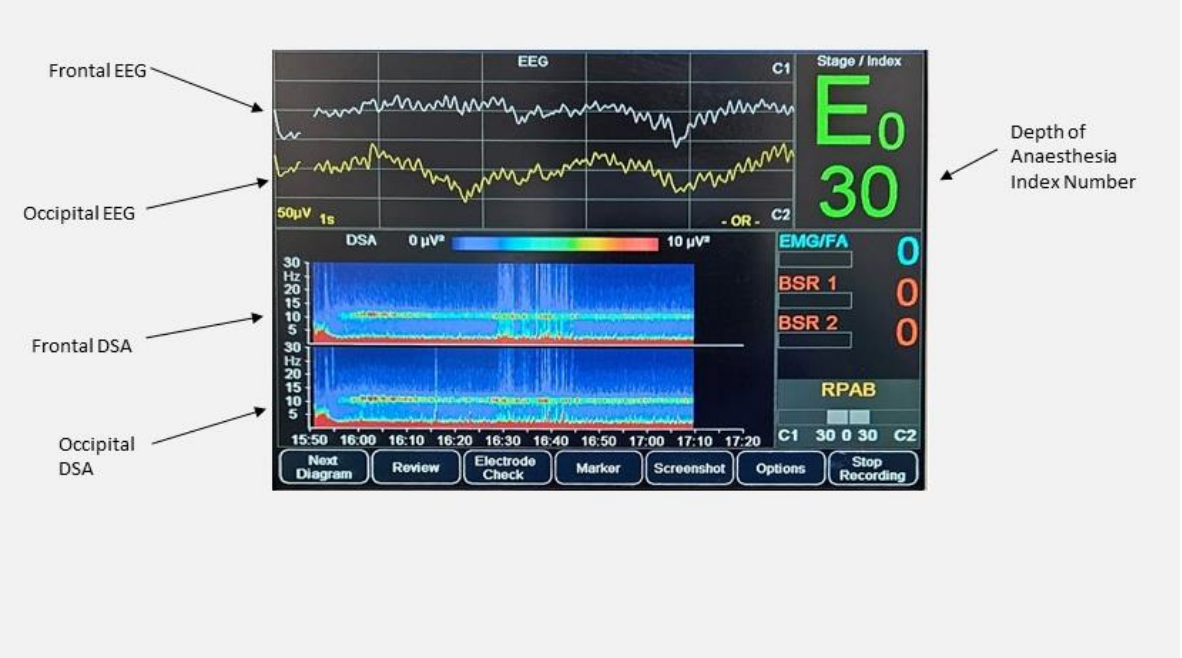

Figure 5.1: Display of frontal and occipital raw EEG and the corresponding digital spectral array.

DSA = Digital spectral array

To accommodate the challenges of traditional EEG acquisition, enquiries were made to the local distributors of frequently used pEEG devices. These enquiries were an effort to identify a pEEG device that could display two channels simultaneously, had an appropriate cable for simultaneous monitoring of frontal and occipital EEG and was affordable. The requirement for simultaneous monitoring of frontal and occipital EEG was to facilitate the continued use of the same device for routine anaesthesia monitoring in a participant, after the preoperative research activities are completed. Responses to the enquiries resulted in the selection of the Narcotrend pEEG device. The Narcotrend device has the added advantage of an age-adjusted algorithm and ability to display the power spectrum in real-time. In addition, there is the concern that the magnitude of the EEG signal measured by scalp electrodes can be affected by skull topography, thickness and patient position[268, 269]. The individual electrodes (as opposed to strips) provided with the Narcotrend monitor allows better precision of electrode placement in our participants.

Considering our requirement that identified biomarkers are easily and readily measurable, a study was conducted on the feasibility of obtaining posterior EEG using a Narcotrend device. If feasible, an exploration of the difference in posterior EEG power (eyes-open and PDR) between people who had POD and those who did not may provide information for or against further exploration of PDR as a biomarker of intrinsic brain vulnerability.

Objectives

Primary objective

Feasibility of obtaining occipital EEG using the Narcotrend processed EEG monitor.

Secondary objectives

Preoperative posterior alpha power assessment:

Compare the preoperative posterior alpha power (eyes-open and eyes-closed) of overtly cognitively intact older people who develop POD to those who do not develop POD. The difference in posterior alpha power between eyes-closed and eyes-open will also be compared between POD and no POD groups.

Preoperative posterior total power assessment:

Compare the preoperative, total power in occipital EEG (eyes-open and eyes-closed) between overtly cognitively intact older people who develop POD and those who do not develop POD

Methods

Study design

A prospective observational study of overtly cognitively intact older people scheduled for moderate or major surgery in a tertiary care hospital. The protocol was registered with Clinicaltrials.gov (NCT05368272) and East of England – Essex Research ethics committee (22/EE/0071) approved the study protocol. This report is structured according to strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

Setting

Participant recruitment was from the preoperative ward or the admissions unit of Queen's Medical Centre (QMC), Nottingham. The recruitment period was 27/01/2023 – 06/12/2023.

Participants

People age ≥ 65 years old presenting to QMC for elective, moderate or major, non-neurosurgery, non-cardiac operations were included in this study. Recruitment was based on availability of researcher, i.e. convenience sampling.

Inclusion criteria were

- Age ≥ 65 years
- Scheduled for elective, moderate/major, non-cardiac, non-neurosurgical surgery

- Ability to give informed consent.

Exclusion criteria were

- Current cognitive impairment (prevalent delirium, cognitive impairment, dementia, AMT < 7)
- Current systemic infection (e.g. COVID)
- Use of EEG modifying medication
- Current or previous neurosurgery
- Neurological disorders (such as stroke, epilepsy, multiple sclerosis, Parkinson's disease, intracranial tumours, head trauma)
- Severe depression
- Palliative surgery.

Research interventions

Postoperative delirium assessments

Participants were assessed twice daily for the first five days after surgery for the occurrence of POD using the 4AT tool. In participants who were positive for POD according to the 4AT tool, the memorial delirium assessment scale (MDAS) was used to confirm POD diagnosis. For POD assessments missed due to non-availability of participant (e.g. off the ward, having clinical interventions or asleep) or researcher, information was obtained from the participant's nurse and the clinical notes for evidence of behavioural changes suggesting POD.

For this study the requirement for a diagnosis of POD was a 4AT score ≥ 4[270], confirmed by an MDAS score ≥ 13 , where possible on at least one occasion[271]. In some participants. The severity of POD precluded MDAS assessment.

EEG recording

EEGs were recorded from all participants using a Narcotrend processed EEG monitor (MT Monitor Technik, Hannover, Germany). After completion of informed consent, participants were positioned semi-recumbent on a trolley or bed in a quiet space. The skin was prepared in accordance with the Narcotrend manufacturer's instructions and adhesive sensors were placed as depicted in figure 5.2. This was to capture frontal and occipital EEG with the reference electrode on the left mastoid.

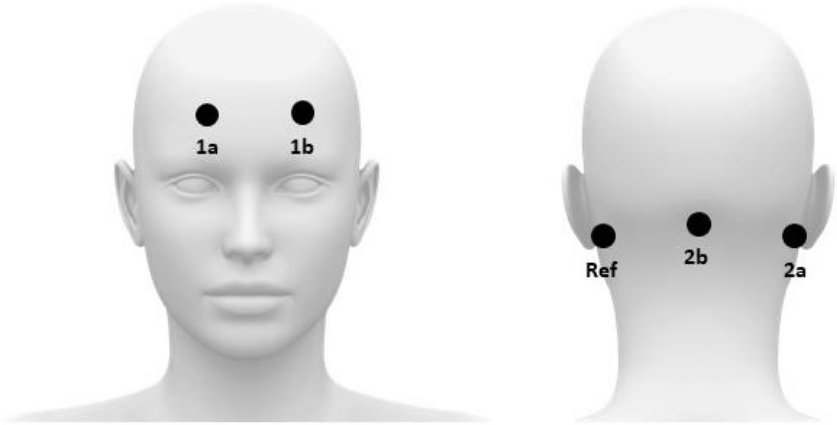

Figure 5.2: Position of scalp electrodes for frontal and occipital EEG recording

1a position = Frontopolar 2 (FP2)

1b position = Frontopolar 1 (FP1)

2a position = Temporal-parietal 10 (TP10)

2b = midline occipital (Oz)

Ref = Temporal-parietal 9 (TP9)

The sensors were connected to the Narcotrend device using a five-electrode lead and EEG recording was commenced. Participants were then instructed open then close, then open their eyes for at least 10 seconds each. Markers to indicate the onset/end of each action (eyes open or eyed shut) were applied to the recording.

In participants that had the baseline intervention performed in theatre, pEEG monitoring was continued for induction of anaesthesia and intraoperative monitoring.

In participants whose baseline EEG was recorded in the admission unit or ward, the monitor was detached after the preoperative EEG recording was completed. The monitor was reattached in the anaesthetic room for induction of anaesthesia, and intraoperative monitoring.

The Narcotrend monitor has a sampling rate of 128 samples/second.

Data processing

While the data from the Narcotrend can be downloaded, it comes in a format that can only be read by special software that is not widely available. We believe this is to protect Narcotrend's proprietary algorithm for calculating depth of anaesthesia index value. A Narcotrend appointed engineer was therefore required to convert the anonymised data, downloaded from the Narcotrend device, to edf and txt format. The conversion software also provides the absolute total power and relative band powers of the main narrow bands e.g. alpha band. The text file contained this information as well as timing of event markers (eyes-open, eyes-closed)

To check for bad EEG segments and estimate the accuracy of the power values provided by the conversion software, the edf files were pre-processed using EEGLAB toolbox[272] in the MATLAB R2019a environment (MathWorks, USA). Pre-processing entailed importing event markers, 0.1Hz and 30Hz high and low pass filters respectively and artefact removal. The resulting waveforms were visually inspected to confirm usability of data in the relevant eyes-open and eyes-closed epochs. For each participant, a 10 – 15 second segment of EEG with good data for eyes-open and eyes-closed epochs was selected and the corresponding power data from the txt file identified. The absolute posterior alpha power in the txt file was converted to absolute values and analysis performed.

Other Variables

Comorbidities: Comorbidities were documented and quantified using the Charlson comorbidity index (CCI).

Frailty assessment: The clinical frailty scale (CFS) score on admission was used.

Statistical methods

The grouping variable was POD or no POD. Feasibility was reported using narrative methods. Group proportions were reported using descriptive statistics (mean +/- standard deviation (SD) or median and interquartile range (IQR) depending on the distribution of data). Comparison of variables between groups was performed using Chi-squared test for categorical variables and Student's T-test/Mann Whitney test for continuous variables. Distribution was assessed using skewness.

The average total power and alpha band power were calculated for each selected epoch and compared between groups using Mann Whitney test. This was performed independently for eyes-open epochs and eyes-closed epochs.

Comparison of the change in power from eyes-open to eyes-closed between POD and no POD groups was performed using repeated measures analysis of variance. This analysis was performed using IBM SPSS for windows vs 29 (SPSS Inc., IBM, USA).

Results

Thirty-two participants were recruited into this study of whom four were withdrawn for the following reasons; cancelled surgery after EEG acquisition – 2, catastrophic surgical complication – 2.

Feasibility

Of the remaining 28 participants, six had poor quality EEG trace. In one participant severe tremor due to anxiety rendered the EEG unreliable. The remaining five had significant amount of artefact resulting in an inability to select 10 – 15-second epochs for either or both eyes-open and eyes-closed states. Raw EEG from which the posterior total and relative alpha power could be assessed were obtained in 22 (79%) of retained participants. There were four participants who had POD and 18 who did not have POD. Baseline characteristics of these participants are depicted in table 5.1. The cognitive status, assessed by the abbreviated mental test score (AMTS) on admission, of POD participants was lower than that of the no POD participants, however all participants had scores within the normal cognition range.

	No POD (n)	POD (n)	p-value
Male/Female	9/9	4/0	0.06
Age in years +/- SD	74 +/- 4	74 +/- 5	0.861
CCI grade	Moderate (3) Severe (15)	Moderate (1) Severe (3)	0.696
AMTS on admission score(n)	8 (1) 9 (3) 10 (14)	8 (2) 9 (1) 10 (1)	0.045
CFS score (n)	2 (8) 3 (6) 4 (2) 5 (1) 6 (1)	2 (1) 3 (2) 4 (1) 5 (0) 6 (0)	0.834
Surgical specialty HPB Vascular Colorectal	 8 6 4	 2 2 0	0.560

Table 5.1 Baseline characteristics of processed EEG and POD participants

CCI Grade = Mild (CCI Score 0 – 2), Moderate (CCI score 3 – 4), Severe (CCI score ≥ 5)

HPB = Hepatobiliary surgery

Posterior alpha power

The average power in the posterior dominant rhythm (alpha power with eyes-closed) was not significantly different between POD and no POD groups. The posterior alpha power with eyes-open was not significantly different between POD and no POD groups. The within-subjects variance was not significant (p = 0.627). The change in posterior alpha power was not significantly different between POD and no POD groups. That said, there were only four participants in the POD group. Please see table 5.2 and figure 5.3 for more details.

	POD (n = 4)	No POD (n = 18)	p-value
Eyes-Open alpha power +/- SD	5.63 +/- 2.66	7.63 +/- 6.62	0.733
Eyes-Closed alpha power +/- SD	4.87 +/- 2.15	5.29 +/- 2.30	0.865
Change in alpha power +/- SD	0.76 +/- 0.61	2.34 +/- 6.28	0.556

Table 5.2: Analysis of posterior alpha rhythm in POD compared to no POD

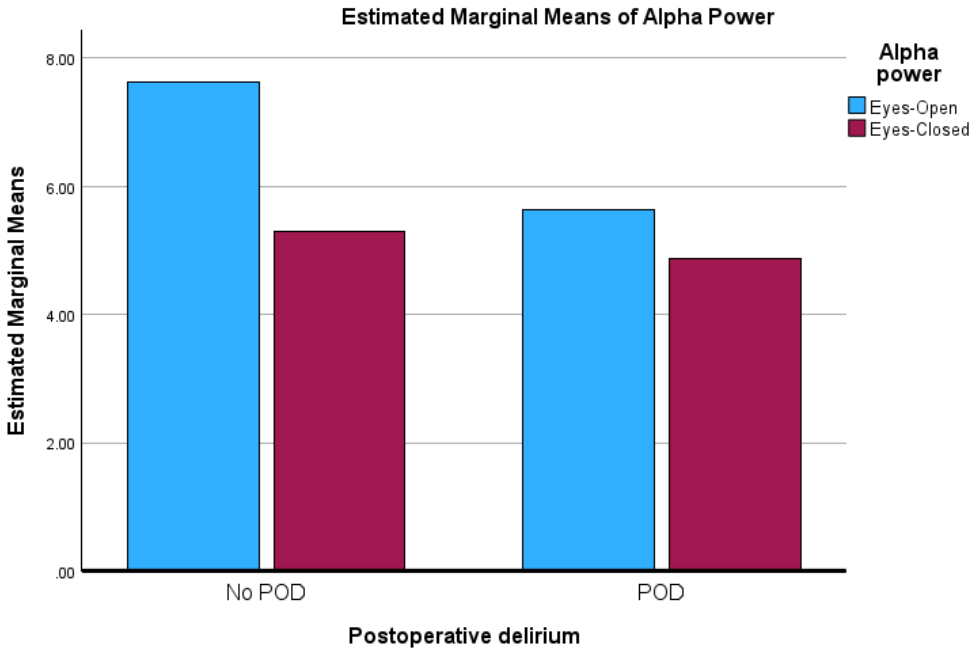

Figure 5.3: Bar chart comparing eyes-open and eyes-closed posterior alpha power between POD and no POD groups.

Posterior total power

The posterior total power (eyes-open or eyes-closed) was not significantly different between POD and no POD groups. The within-subjects variance was not statistically significant (p = 0.438). The change in posterior total power from eye-open to eyes-closed was not significantly different between POD and no POD. Please see Table 5.3 and Figure 5.4 for more details.

	POD (n = 4)	No POD (n = 18)	p-value
Eyes-open total power	285 +/- 189	558 +/- 544	0.340
Eyes-closed total power	252 +/- 205	294 +/- 304	0.799
Change in total power	33 +/- 200	264 +/- 570	0.378

Table 5.3: Analysis of posterior total power comparing POD to no POD

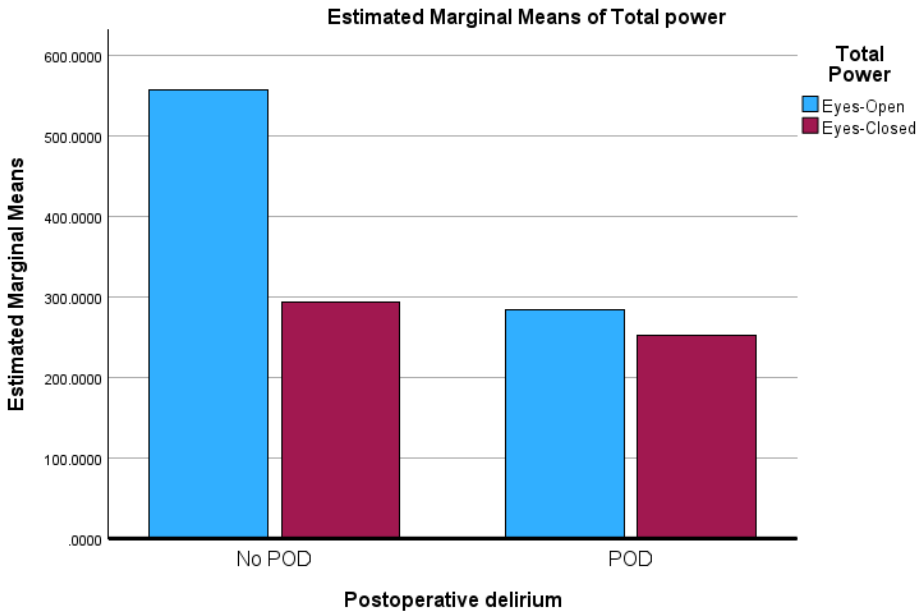

Figure 5.4: Bar chart comparing eyes-open and eyes-closed posterior total power between POD and no POD groups

Discussion

Our findings suggest that it is feasible to obtain raw EEG data that is fit for analysis, using the Narcotrend processed EEG monitor. As far as we are aware this is the first study using a processed EEG monitor to capture raw EEG for subsequent analysis of the posterior EEG

power. Given this, our ability to analyse the EEG in 79% of participants with preoperative monitoring is encouraging.

However, there was no significant difference in the posterior alpha rhythm, eyes-open or eyes-closed state, between POD and no POD groups. The change in power between eyes-open and eyes-closed states was also not statistically significant. The findings were similar for the posterior total power.

It may be that the findings of our secondary outcomes are true effects. However, given the limited number of participants in this study, and the paucity of participants with POD, there is the potential that this may be a type II error. This is not particularly surprising since the study was not powered to detect differences in power. That said, the trend in our data suggests that eyes-open and eyes-closed posterior alpha and total power may be lower in people who develop POD compared to those who do not. There is also a trend suggesting that the change in posterior alpha and total power between eyes-open and eyes-closed may be attenuated in people who subsequently develop POD.

We are aware of a study that explored the postoperative posterior EEG and POD[273]. The study was a sub-study of the ENGAGES trial[5]. Thirty-one participants, of whom 18 had POD, had the posterior EEG acquired using an EEG device (not a processed EEG device). Similar to our study, five participants had poor data and were excluded. Their regression analysis suggests that postoperative, resting state, posterior dominant rhythm is moderately associated with POD severity. Unfortunately, some recordings were obtained on days on which POD occurred making the discrimination between predictive and diagnostic biomarker unclear.

Our study has some limitations. The limited number of participants and the low number of POD precludes any significant conclusions. However, feasibility of using a routinely used bedside monitor to obtain raw EEG for analysis was confirmed. The majority of our participants had high risk surgery. The resulting attrition in the number of participants that completed the study due to surgical complications was unfortunate. However, these are the procedures associated with a higher risk of POD thus inclusion is valid and relevant[26]. The inability to extract raw EEG from the Narcotrend monitor in a format that can be directly read by widely available software is also problematic. While the need to protect the proprietary algorithms for calculating depth of anaesthesia index is appreciated, the need to send the data away for conversion to an accessible format curtails the real-time applicability of power analysis on a wider scale. We are however appreciative of the time and effort the Narcotrend engineer put into converting the data for this study.

Conclusion

Acquiring raw posterior EEG from the Narcotrend EEG monitor for subsequent analysis is feasible. There were no differences in the posterior alpha power, total power and power transition from eyes-open to eyes-closed, although a trend was observed. Future studies

that are powered for the differences in power of the posterior dominant rhythm between people with POD and no POD are required.

Intrinsic Vulnerability – Inflammation chapter

Inflammatory mediators in older hip fracture surgery patients and postoperative delirium

Background

The systematic review on preoperative inflammatory mediators and postoperative delirium (POD) found an association between high preoperative blood interleukin 6 (IL-6) levels and POD[164]. Other mediators explored in the review included C reactive protein (CRP), tumour necrosis factor alpha (TNF-α), interleukins 8 and 10 (IL-8 and IL-10), insulin-like growth factor 1 (IGF-1), cortisol and neopterin.

That high preoperative IL-6 is associated with increased incidence of POD is not surprising given that, although IL-6 at physiologic levels is neurotrophic, dysregulated production can be devastating[53, 274]. That said, this is a group-based result rather than an individual patient outcome. The individual subject effect is particularly important for development of POD risk prediction tools. Understanding the variety, at the individual subject level, of the association between IL-6 and POD is made complex by the pleiotropic property of IL-6[48], interactions between IL-6 and other cytokines[50], and influence of soluble interleukin 6 receptor (sIL-6R)[55]. Signalling by IL-6 is mediated, via its complex with sIL-6R, by binding to transmembrane glycoprotein 130 (gp130). Neurons do not have membrane bound IL-6 receptor and are thus dependent on the availability of sIL-6R[275]. From animal studies, sIL-6R enhances the neurotrophic effect of IL-6 at physiologic levels. Conversely, trans-signalling, mediated by the IL-6/sIL-6R complex, may be responsible for some neurotoxicity of IL-6[276]. Consistent with this, human studies have demonstrated high serum sIL-6R levels in treatment resistant depression[277]. Interestingly, IL-6 and TNF-α levels were not associated with treatment resistant depression in the same study. In addition, a study on cognitive impairment in older people found an association between higher sIL-6R levels and lower cognitive performance[278]. Finally, the impact of inflammaging on IL-6 levels must also be considered. While inflammaging is associated with increasing age, it occurs at different rates in different people. The impact of inflammaging may be reflected, to a degree, in the extent of frailty and comorbid state of the individual[279-281].

A surprising finding, in the systematic review, was the lack of a protective association between preoperative IGF-1 and POD. IGF-1 is important for neurogenesis and modulating neuroinflammation[75, 282]. Of note, impairment of intracranial IGF signalling and reduced levels of IGF-1 are implicated in Alzheimer's disease[283].

The studies identified in the systematic review used blood (serum/plasma) levels of IGF-1. Circulating IGF-1 is bound to carrier proteins, predominantly insulin-like growth factor binding protein 3 (IGFBP-3)[75]. Binding prolongs the half-life of IGF-1, provides a reservoir and facilitates transport. However, binding to IGFBP-3 may enhance or inhibit the effect of IGF-1[284]. Adding to the complexity is the interaction between TNF-α and IGF-1. TNF-α may inhibit the neurotrophic property of IGF-1 or induce IGFBP-3 gene expression[285]. Also in the older person, IGF-1 and IGFBP-3 slowly decline with increasing age albeit at individual rates[74].

Postoperative cytokine levels have also been implicated in the aetiology of postoperative delirium[68, 69, 71]. The scale of the cytokine response to the anaesthesia/surgical intervention may be influenced by the magnitude of surgery (such as laparoscopic vs open surgery)[46], or individual patient factors e.g. inflammatory gene polymorphisms[286]. Surgery induces a host of inflammatory mediators such as TNF-α, Cortisol and Interleukins; however, the level of IL-6 has been consistently associated with the magnitude of surgery, with peak levels occurring 4 – 48 hours after surgery[45, 287]. Specific to hip fracture surgery, there is an association between early postoperative IL-6 magnitude and type of surgery performed[288].

Hip fracture surgery provides a special case with regards to cytokine dynamics. Higher baseline inflammatory mediators may be associated with an increased risk of subsequent hip fracture, particularly fragility fractures[289]. Furthermore, the inflammatory response is further triggered by the hip-fracturing injury, prior to surgery. The added inflammation due to subsequent hip fracture surgery must be interpreted in the context of on-going injury-induced, as well as baseline, inflammation. Incidentally, hip fracture surgery is the most frequent indication for acute major surgery in the older person (i.e. age ≥ 65 years) and is associated with a significant incidence of POD (approximately 25%)[290].

In this study, the role of the trajectory of IL-6/IGF-1 across hip fracture surgery in the development of POD was explored. The impact of preoperative IL-6/IGF-1 on the incidence of POD was also assessed. Finally, the impact of interactions between IL-6/IGF-1 and proposed potential modifiers of their actions on the incidence of POD was also assessed. Proposed modifiers of IL-6 in this study are sIL-6R and TNF-α; proposed for IGF-1 is IGFBP-3 and TNF-α. The impact of established modifiers of the inflammatory response e.g. frailty status, age and comorbidities, will also be adjusted for.

Objectives

Primary

Assess the ability to predict POD by the change in blood IL-6/IGF-1 levels across the anaesthesia/surgical intervention, adjusted for established and proposed modifiers, in cognitively intact older people undergoing hip fracture surgery.

Secondary

Assess the ability to predict POD by preoperative blood IL-6/IGF-1 levels, adjusted for established and proposed modifiers, in cognitively intact older people undergoing hip fracture surgery.

Assess if interactions between preoperative IL-6/IGF-1 and proposed modifiers are predictive of POD.

Methods

Study design

Prospective observational pilot study on cognitively intact older people (age ≥ 65 years) undergoing hip fracture surgery in a secondary care centre. The study was approved by NHS HRA REC (Reference 21/LO/0850). The structure of this report was guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

Participants were recruited from the trauma wards and the emergency department of Queen's Medical Centre, Nottingham. Recruitment occurred between June 2022 and March 2024.

Participants

Patients presenting to the institution with primary hip fracture amenable to surgical fixation were screened for this study. Inclusion criteria were age ≥ 65 years old, listed for primary, unilateral hip fracture surgery, and ability to give written informed consent. Exclusion criteria were declined participation, concurrent cognitive impairment (e.g. prevalent delirium, abbreviated mental test score on admission ≤ 7, mild cognitive impairment and dementia), systemic infection (e.g. COVID-19), neurological factors that could influence the risk of postoperative delirium (e.g. overt stroke, dementia, multiple sclerosis, Parkinson's disease, intracranial tumours, neurosurgery and head trauma), current participation in a clinical trial of investigational medicinal product (CTIMPS), use of immunosuppressant medication, multiple injuries and not expected to survive the early postoperative period.

Inflammatory mediator measurement

Preoperative and postoperative blood samples, from which preselected inflammatory mediators were measure, were drawn from participants. Preoperative blood samples were taken in the anaesthetic room just prior to surgery. Postoperative samples were taken on one or two occasions depending on availability (difficulty of venepuncture or time of night). Timings of postoperative blood samples were 6 – 12hrs and/or 21 – 26 hrs after surgery.

Blood samples, taken in lithium heparin BD vacutainer® tubes, were centrifuged using a Jouan BR4i device (Jouan, France) at 2500 rpm for 7 minutes. Aliquots of plasma were extracted and stored at –80°C. The samples were batch processed for the preselected mediators. Mediators measured included IL-6, sIL-6R, TNF-α, IGF-1 and IGFBP-3. Enzyme linked immunosorbent assay (ELISA) using the mediator-specific Quantikine ELISA kit (R&D systems, Minnesota, USA) was performed by a senior laboratory technician. Each assay was validated using a control. Samples were tested in duplicates to ascertain accuracy of measurement. In the event of divergent results of >10% for a sample, a third test was conducted to clarify results.

Postoperative delirium assessments

Delirium assessments were performed twice daily for the first five days after surgery using the 4AT tool and memorial delirium assessment scale (MDAS). If participants were not available (asleep or off the ward) or on the rare occasion when the researcher was unavailable, information was obtained from the participant's nurse and the clinical notes for evidence of behavioural changes suggesting POD.

Variables

Diagnostic criteria for POD: A diagnosis of POD was made if a participant's 4AT score was ≥ 4[270]. This was confirmed with an MDAS of ≥ 13[271]. In some MDAS was not possible due to severity of delirium symptoms.

Perioperative dexamethasone: Dexamethasone, a steroid and anti-inflammatory drug, is often used as a prophylactic anti-emetic in the perioperative period. The use and dose of dexamethasone was documented.

Comorbidities: This was recorded and quantified using the Charlson comorbidity index (CCI).

Frailty assessment: The clinical frailty scale (CFS) score on admission was used.

Data sources

Inflammatory mediator and POD assessment - Research activity

Comorbidities, dexamethasone dose - Participants' clinical records

Study size

A sample size of 45 – 60 participants was the pragmatic choice for this hypothesis supporting/generating study. Assuming an estimated incidence of delirium of around 20-30% the expected incidence of POD was 9 – 18 people. This sample size is appropriate for studies such as these, where multicentre replication of significant findings would be required before definitive conclusions are drawn[259].

Statistical methods

Participant groups are POD and no POD. Group proportions are reported using descriptive statistics; mean +/- standard deviation or median (interquartile range) depending on the distribution of the data. Distribution was determined by skewness. Comparison of baseline characteristics between groups were analysed using chi squared test (for categorical data) and Student's T-test/Mann-Whitney for continuous variable. Analysis of the association between the independent variables and incidence of POD was by logistic regression analysis.

Logistic regression analysis structure

Mediator and adjusted analysis

Model 1: Analysis of prediction of POD by IL-6 (or change in) and IGF-1 (or change in) individually i.e. without accounting for any other variables (crude odds).

Model 2: Model 1 adjusted for covariates identified as established modifiers of POD, IL-6 or IGF-1. These were age, comorbidity, frailty and dexamethasone dose.

Model 3: Model 2 + other relevant inflammatory mediators. For the IL-6 analysis, sIL-6R and TNF-α were added to the regression model. For IGF-1, IGFBP-3 levels were adjusted for.

Interaction analysis

Analysis of prediction of POD by interactions of IL-6/IGF-1 with relevant inflammatory mediators. The interaction term for this model is multiplication of the participant's IL-6 and other mediator's value, e.g. IL-6 x TNFα.

Prior to binary logistic regression, the data were tested for assumptions to ensure appropriateness of analytic method. Correlation of variables was assessed using Spearman correlation. Outliers were tested for using the Chi squared test of the Mahalanobis distance. Linearity of each independent variable and its natural log was tested using the Box-Tidwell procedure. Goodness of fit was tested using the Hosmer-Lemeshow test.

Receiver operating characteristic (ROC) curve analysis was performed for any significant predictors of POD. Maximised Youden's index was used to identify possible cut-off points.

Mediator levels taken 6 – 12 hrs post-surgery are referred to as '12hr' and mediator levels taken 21 -26 hours after surgery are '24hr'.

All mediators were above the lower limit of the assay range for the relevant kit.

Statistical analysis was performed using IBM SPSS for windows vs 29 (SPSS Inc., IBM, USA).

Outcome

Primary outcome

The prediction of POD by the change in IL-6 or IGF-1 across surgery at '12hr' and '24hr' after surgery adjusted for established and proposed modifiers.

Secondary outcomes

Prediction of POD by preoperative IL-6 or IGF-1 levels adjusted for established and proposed modifiers.

Prediction of POD by interactions between IL-6/IGF-1 and proposed modifiers.

Results

Forty-nine people were recruited to this study. Two were excluded due to inadvertent omission of preoperative blood sample. A further two participants had acute clinical deterioration in the early postoperative period (myocardial infarction and multi-organ failure) and were thus excluded. Of the remaining 45 participants, 9 experienced POD. There were no significant differences between POD and no POD group with regards to baseline and surgical factors (Table 6.1).

	POD n = 9	No POD n = 36	p-value
Male/Female	6/3	13/23	0.097
Age in years mean +/- SD	79+/- 9	82 +/- 6	0.237
AMTS score (n)	8 (1) 9 (3) 10 (5)	8 (3) 9 (7) 10 (26)	0.613
CCI grade (n)	Mild (1) Moderate (5) Severe (3)	Mild (1) Moderate (20) Severe (15)	0.535
CFS score (n)	2 (3) 3(1) 4 (4) 5 (1)	2(6) 3 (11) 4(13) 5 (3) 6(2) 7(1)	0.705
Interval between injury and surgery in days Median (IQR)	1 (1 - 3)	2(1 - 3)	0.532
Mode of Anaesthesia (n)	General (5) Spinal (4)	General (18) Spinal (17) Peripheral nerve blocks (1)	0.858
Procedure performed (n)	Cannulated screw (1) Dynamic hip screw (1)	Cannulated screw (3) Dynamic hip screw (11)	0.446

	Intramedullary nail (2) Hemiarthroplasty (4) Total hip replacement (1)	Intramedullary nail (2) Hemiarthroplasty (18) Total hip replacement (2)	
Duration of surgery in minutes	74 +/- 30	58 +/- 20	0.173
Intra-op Dexamethasone (n)	Yes (4)	Yes (9)	0.250
Dexamethasone dose in mg Median (IQR)	0 (0 – 6.6)	0 (0 – 1.65)	0.262

Table 6.1: Comparison of participants' characteristics POD vs no POD

CCI Grade = Mild (CCI Score 0 – 2), Moderate (CCI score 3 – 4), Severe (CCI score ≥ 5)

Impact of change in IL-6 or IGF-1 levels across surgery on incidence of postoperative delirium

Thirty-seven participants had '12hr' postoperative inflammatory mediator levels of whom eight experienced POD.

Thirty-five participants had '24hr' postoperative inflammatory mediator levels of whom eight experienced POD.

Dynamics of interleukin 6 and POD

Difference in IL-6 between '12hr' and preoperative levels

Direction of change in IL-6 levels at '12hr'

IL-6 levels at '12hr' were higher than preoperative IL-6 in 30 of 37 participants (table 6.2). There was no significant difference between POD and no POD regarding direction of IL-6 change at '12hr' (p = 0.25)

	IL-6 lower at '12hr'	IL-6 higher at '12hr'

POD	3	5
No POD	4	25

Table 6.2: Direction of change in IL-6 levels comparing '12hr' sample to preoperative sample.

Prediction of POD by change in IL-6 at '12hr'

The difference between preoperative IL-6 levels and '12hr' IL-6 was not predictive of POD (Table 6.3).

Change in IL-6 at '12hr' model	Beta	Odds ratio	95% confidence interval
Model 1	-0.009	0.991	0.979 – 1.003
Model 2	-0.015	0.985	0.967 – 1.003
Model 3	-0.015	0.985	0.965 – 1.005

Table 6.3: Analysis for POD prediction by change from preoperative levels of IL-6 at '12hr' after surgery.

Difference in IL-6 between '24hr' and preoperative levels

Direction of change in IL-6 levels at '24hr'

IL-6 levels at '24hr' were higher than preoperative IL-6 in 26 of 35 participants (Table 6.4). There was no significant difference between POD and no POD regarding direction of IL-6 change at '24hr' ($p = 0.668$)

	IL-6 lower at '24hr'	IL-6 higher at '24hr'
POD	2	6
No POD	7	20

Table 6.4: Direction of change in IL-6 levels comparing '24hr' sample to preoperative sample.

Prediction of POD by change in IL-6 at '24hr'

The analysis of the difference between preoperative IL-6 levels and '24hr' IL-6 was not predictive of POD (Table 6.5).

Change in IL-6 at '24hr' model	Beta	Odds ratio	95% confidence interval
Model 1	0.001	1.001	0.991 – 1.011
Model 2	0.003	1.003	0.992 – 1.015
Model 3	0.010	1.010	0.994 – 1.025

Table 6.5: Analysis for POD prediction by change from preoperative levels of IL-6 at '24hr' after surgery.

Trajectory of IL-6

In our study, IL-6 was available at all three time points in 27 participants of whom 7 had POD. The plots below demonstrate the trajectories of IL-6 across the time periods in individual participants for the whole cohort (figure 6.1), No POD (figure 6.2) and POD (figure 6.3). The direction change was not significantly different between POD and no POD.

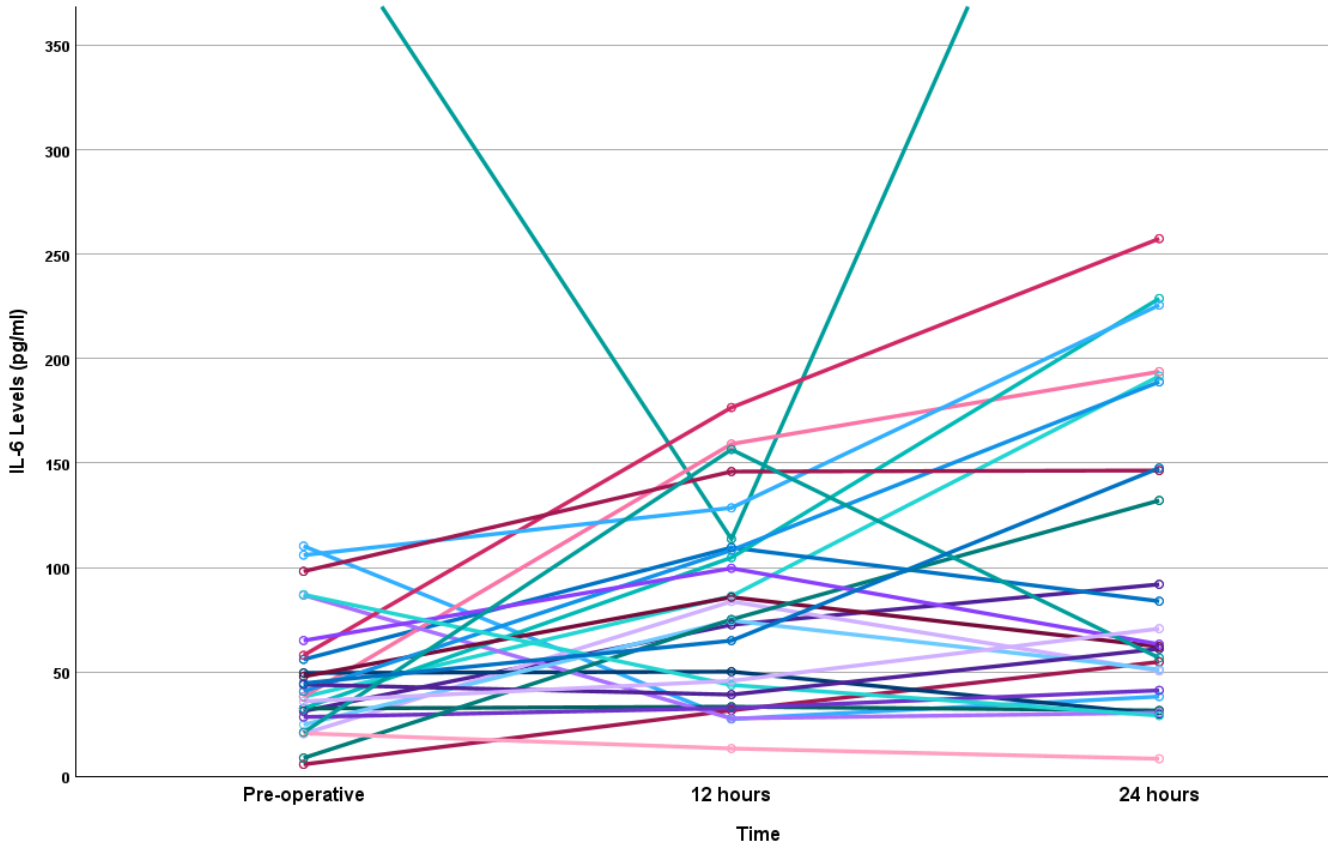

Figure 6.1: Trajectory of IL-6 in all participants across the three measurement periods.

Each coloured line represents the trajectory of one participant.

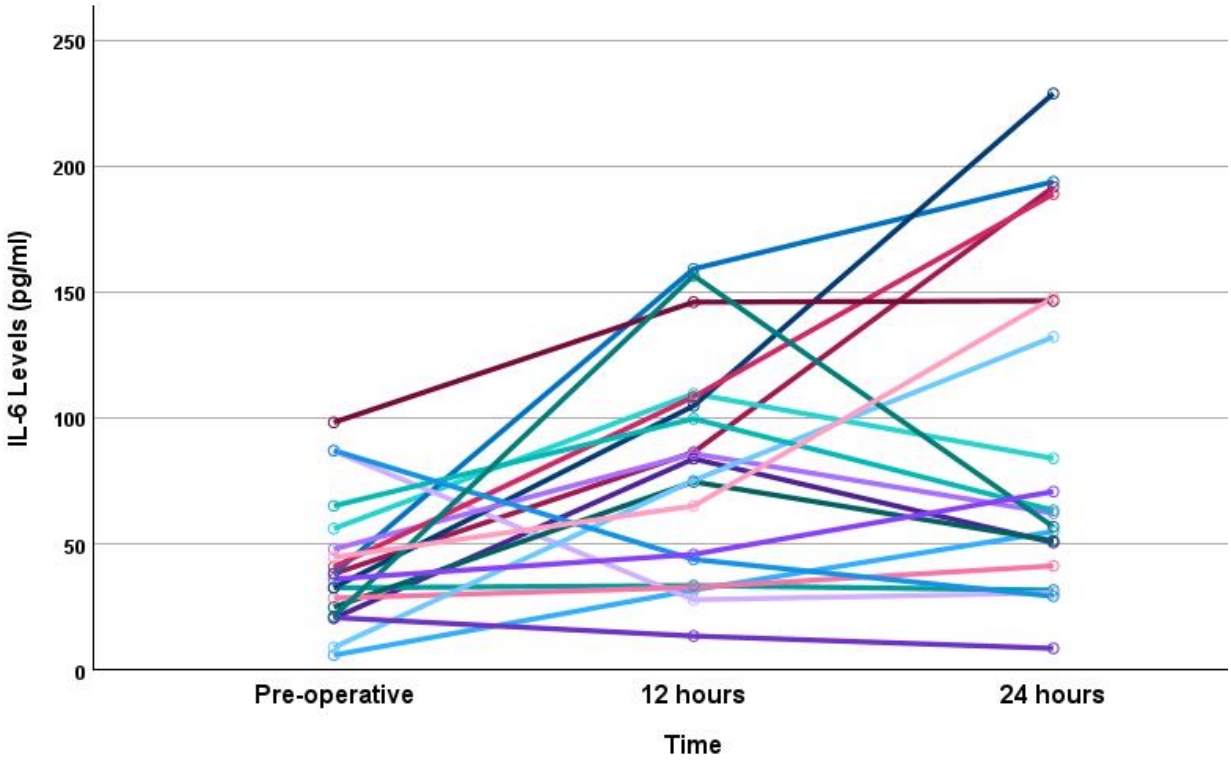

Figure 6.2: Trajectory of IL-6 in participants who did not experience POD across the three measurement periods.

Each coloured line represents the trajectory of one participant.

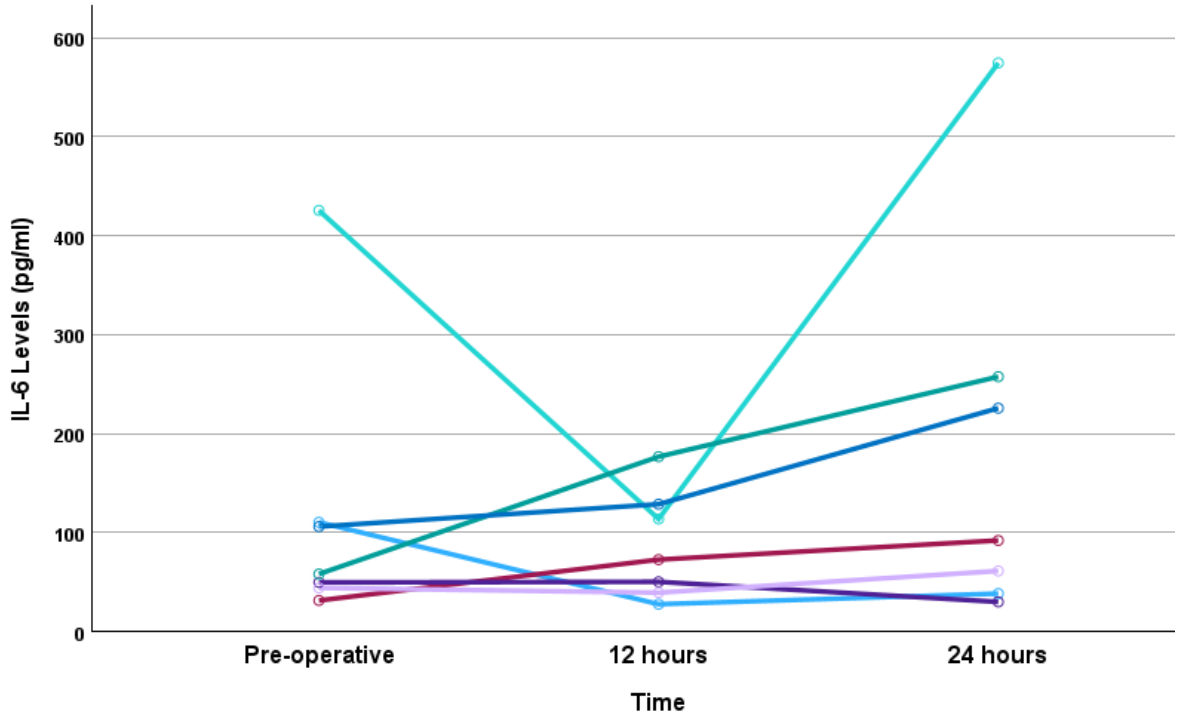

Figure 6.3: Trajectory of IL-6 in participants who experienced POD across the three measurement periods.

Each coloured line represents the trajectory of one participant.

Dynamics of insulin-like growth factor 1 and POD

Difference in IGF-1 between '12hr' and preoperative levels

Direction of change in IGF-1 levels at '12hr'

IGF-1 levels at '12hr' were higher than preoperative IGF-1 levels in 13 of 37 participants (table 6.6). There was no statistically significant difference between POD and no POD regarding direction of change in IGF-1 levels at '12hr' (p = 0.25).

	IGF-1 lower at '12hr'	IGF-1 higher at '12hr'
POD	7	1
No POD	17	12

Table 6.6: Direction of change in IGF-1 levels comparing '12hr' sample to preoperative sample.

Prediction of POD by change in IGF-1 at '12hr'

The analysis of the difference between preoperative IGF-1 levels and ‘12hr’ IGF-1 was not predictive of POD (table 6.7).

Change in IGF-1 at ‘12hr’ model	Beta	Odds ratio	95% confidence interval
Model 1	-0.017	0.983	0.879 – 1.099
Model 2	0.000	1.000	0.861 – 1.161
Model 3	0.006	1.006	0.861 – 1.176

Table 6.7: Analysis for POD prediction by change from preoperative levels of IGF-1 at ‘12hr’.

Difference in IGF-1 between ‘24hr’ and preoperative levels

Direction of change in IGF-1 levels at ‘24hr’

IGF-1 levels at ‘24hr’ were higher than preoperative IGF-1 levels in 14 of 35 participants (table 6.8). There was no statistically significant difference between POD and no POD regarding direction of change in IGF-1 levels at ’24hr’ (p = 0.659).

	IGF-1 lower at ‘24hr’	IGF-1 higher at ‘24hr’
POD	5	3
No POD	16	11

Table 6.8: Direction of change in IGF-1 levels comparing ‘24hr’ sample to preoperative sample.

Prediction of POD by change in IGF-1 at ‘24hr’

The analysis of the difference between preoperative IGF-1 levels and ‘24hr’ IGF-1 was not predictive of POD (table 6.9).

Change in IGF-1 at ‘24hr’ model	Beta	Odds ratio	95% confidence interval
Model 1	-0.019	0.981	0.917 – 1.050
Model 2	-0.005	0.995	0.911 – 1.088
Model 3	-0.012	0.988	0.900 – 1.086

Table 6.9: Analysis for POD prediction by change from preoperative levels of IGF-1 at ‘24hr’.

Preoperative mediators and POD

Forty-five participants had preoperative IL-6 and IGF-1 levels of whom nine experienced POD.

Preoperative interleukin 6 and postoperative delirium

In this analysis, preoperative IL-6 was moderately predictive of POD. In the unadjusted analysis, the Nagelkerke R^2 was 0.276, unadjusted odds ratio (95% CI) is 1.029 (1.004 – 1.056) and p = 0.025. Adjustment for covariates (age, comorbidities, dexamethasone dose and frailty) and covariates with modifiers (sIL-6R and TNF-α) did not significantly improve the predictive estimate of preoperative IL-6 (table 6.10).

Preoperative IL-6 models	Beta	Odds ratio	95% confidence interval
Model 1	0.029	1.029	1.004 – 1.056
Model 2	0.042	1.043	1.007 – 1.079
Model 3	0.041	1.042	1.005 – 1.080

Table 6.10: Analysis for POD prediction by preoperative IL-6 levels

Given that preoperative IL-6 may be predictive of POD, receiver operating characteristic (ROC) curve analysis was performed (Figure 6.4). The area under the curve (AUC) was 0.753. The maximum Youden's index of 0.444 suggests two cut-offs. 42.86 pg/ml with sensitivity of 78% and specificity of 67% or 48.68 pg/ml with a sensitivity of 67% and a specificity of 78%.

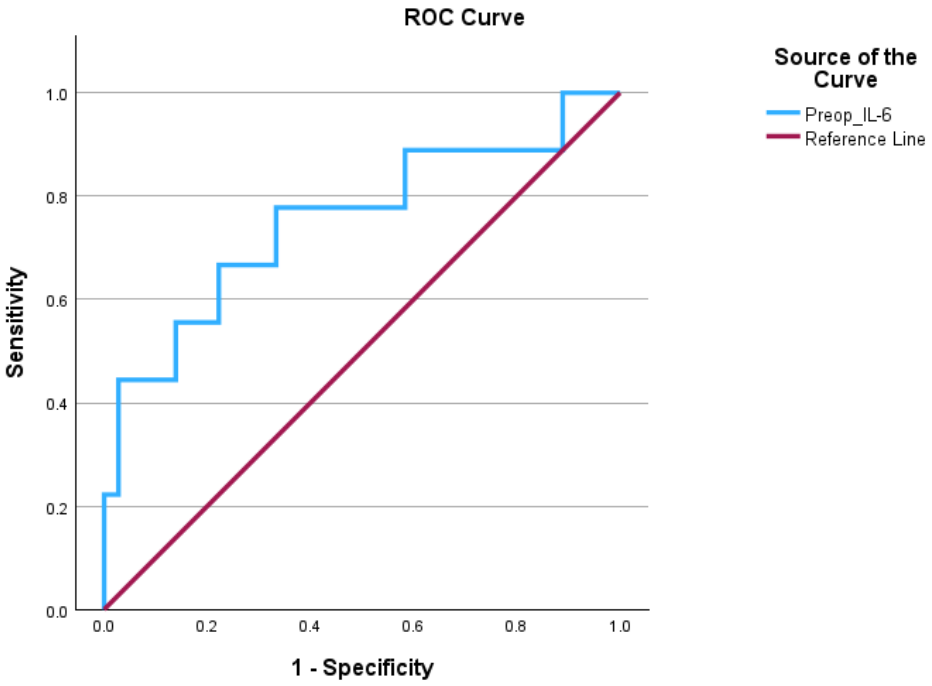

Figure 6.4: Receiver operating characteristic curve for preoperative IL_6 as a predictor of postoperative delirium in older hip fracture surgery patients.

Preoperative Insulin-like growth factor 1 and postoperative delirium

In this analysis, neither unadjusted nor adjusted preoperative IGF-1 was not predictive of POD (table 6.11).

Preoperative IGF-1	Beta	Odds ratio	95% confidence interval
Model 1	-0.015	0.985	0.940 – 1.032
Model 2	-0.025	0.976	0.924 – 1.030
Model 3	-0.027	0.974	0.917 – 1.034

Table 6.11: Analysis for POD prediction by preoperative IGF-1 levels

Preoperative mediator interactions and POD

Interleukin 6 interactions

Interaction between IL-6 and sIL-6R was not predictive of POD

Interaction between IL-6 and TNF-α marginally improved the predictive estimate of the null model.

Insulin-like growth factor 1 interactions

Interaction between IGF-1 and IGFBP-3 was not predictive of POD

Interaction between IGF-1 and TNF-α was not predictive of POD

Preoperative Interaction model	Beta	Odds ratio	95% confidence interval
IL-6*sIL-6R	0.000	1.000	1.000 – 1.000
IL-6*TNFα	0.001	1.001	1.000 – 1.002
IGF-1*IGFBP-3	0.000	1.000	1.000 – 1.000
IGF-1*TNFα	0.000	1.000	0.998 – 1.002

Table 6.12: Predictive estimates of POD by preoperative mediator interactions compared to the null model.

Discussion

In this cohort of cognitively intact older people undergoing hip fracture surgery, the difference between preoperative IL-6 or IGF-1 levels and levels at '12hr' or '24hr' after surgery did not predict the incidence of POD. Adjusting for the effect of established modifiers i.e. age, comorbidities, frailty and dose of dexamethasone did not result in prediction of POD. Similarly, adjustment for proposed modifiers i.e. time-specific change in soluble IL-6 receptor, TNF-α and IGFBP-3 (as relevant) did not improve prediction of POD.

However, preoperative IL-6 emerged as a potential predictor of POD with a moderate effect. The suggested cut-off point is 42.86 pg/ml with sensitivity of 78% and specificity of 67%. The AUC of 0.753 suggests fair discrimination between POD and no POD[291]. This effect was not significantly altered by adjusting for established and proposed modifiers.

Preoperative IGF-1 level, alone or after adjustment for established and proposed modifiers, was not predictive of POD.

Interactions between IL-6 and sIL-6R/TNF-α did not contribute to POD prediction. Similarly, interactions between IGF-1 and IGFBP-3/TNF-α did not contribute to POD prediction.

The rationale for the inflammatory mediators chosen for this study is supported by literature[53, 292]. Dysregulated IL-6 has been implicated in diverse neurologic diseases, e.g. Alzheimer's disease and Parkinson's disease. Also, our systematic review identified IL-6 as a potential predictor of POD. Examination of the kinetics of IL-6 after hip fracture surgery, i.e. rises soon after surgery, peaks at 24 – 48 hours and may persist for up to 5 days[288, 293], also support notion that IL-6 may play a role especially since POD occurs during the first 7 days after surgery[196]. The choice of moderators of IL-6, i.e. sIL-6R and TNF-α is also supported by research[49, 55]. There was a concern regarding potential correlation between IL-6 and TNF-α. Analysis of our data yielded a Spearman correlation coefficient between preoperative IL-6

and TNF-α of 0.582 which suggests some degree of collinearity. However, in the assumptions of logistic regression, the threshold for collinearity is 0.8, thus the inclusion of TNF-α is valid[294].

The choice of IGF-1 as a second mediator is a little more complex, especially since the systematic review did not identify an association between IGF-1 and POD. However, IGF-1 is largely neuroprotective via modulation of microglia, preservation of the blood-brain barrier and reduced cytokine expression[282]. The absence of a protective effect regarding POD in the review, if the Neuroinflammatory hypothesis has merit, suggests confounders must be considered. The modifying effects of IGFBP-3 and TNF-α on IGF-1 are well described[75, 284, 285].

There is a paucity of studies on trajectory of inflammatory mediators across hip fracture surgery and POD. A study on 41 older hip fracture patients suggested an association between the IL-6 trajectory and postoperative cardiovascular complications[43]. In that study, the kinetics of IL-8 differed between delirium and no delirium groups. Of note, the cytokines were measured preoperatively, at 48 – 60 hours and at subsequent time points. Unfortunately, due to the dynamics of IL-6 after surgery, the timing of the first postoperative blood sample may have been too late to capture the early dynamics of IL-6. In another study on older hip fracture patients, cytokines were measured preoperatively and several postoperative days[68]. While that study found an association between high IL-6 and POD, the impact of the scale of change in IL-6 levels across surgery was unstated. In addition, that study included participants with prevalent delirium, making understanding of the dynamics with POD (incident delirium) difficult to unravel.

There is some literature on the association between the trajectory of inflammatory mediators and postoperative delirium in other surgical cohorts[31, 187, 295]. In the successful aging after elective surgery cohort, people age ≥ 70 years undergoing elective surgery, the trajectory of IL-6 showed a mean rise, with a peak level achieved on postoperative day 2[31]. Higher values of IL-6 on day 2 were associated with POD suggesting a higher trajectory. However, the absolute values of differences from preoperative levels were not investigated. In another study on cardiac surgery patients, the change in IL-6 levels at 18 hours after surgery was a predictor of POD (adjusted odds - 2.97 (1.20 – 7.31))[189]. Unfortunately, 'change in' was not clearly defined although my assumption is change from baseline levels. Interestingly, the authors assessed the trend in IL-6 in POD group vs no POD group using multivariate repeated measures analysis of variance (ANOVA). This is probably useful demonstrating an association. However, for the purpose of biomarker identification, and given that POD is the dependent variable, regression analysis is our preferred method[296]. Incidentally, applying repeated measures ANOVA to our data, the between-subjects analysis yielded a p value of 0.054. A recent study on people age > 60 years undergoing major lower limb surgery (elective and hip fracture surgery) investigated the trajectory of inflammatory mediators and POD[295]. In that study, participants with fluctuating higher levels of IL-6 or sIL-6R trajectory were more likely to have POD. Unfortunately, the interaction between IL-6 and sIL-6R does not appear to have been investigated. In our study, the absolute change in levels of IL-6 or IGF-1, adjusted for established modifiers, across surgery were not predictive of POD. It could be argued that our sample size was insufficient to identify a difference. That

argument would be valid if this was purely a statistical exercise. However, for individual patient applicability, this researcher feels there needs to be readily measurable predictors of POD that have individual patient applicability.

An interesting finding in this study was the inconsistent trajectory of IL-6 across surgery. Previous authors have reported a rise in inflammatory mediators after hip fracture surgery[43, 185, 293]. In Beloosesky et al's study on older hip fracture patients there was an increase in IL-6 at 48 hours after hip fracture surgery. Sun et al reported an increase starting on day 1. Similarly, the mean IL-6 in both our no POD and our POD groups were high at '24hr' compared to preoperative levels. However, examination of individual patient's trajectories in our study demonstrated some had reduced '24hr' IL-6 levels compared to baseline. While this finding was not significantly different in the POD vs no POD groups, it does highlight the need to consider each individual's mediator responses in research on POD predictors/biomarkers.

The finding that preoperative IL-6 is a potential predictor of POD supports the result of our systematic review. It was surprising that controlling for sIL-6R levels did not improve the performance of preoperative IL-6. Further, the analysis of interaction between IL-6 and sIL-6R was not predictive of POD. The premise that IL-6 requires sIL-6R for trans-signalling, resulted in the expectation that controlling for, or exploring an interaction with, sIL-6R would augment the predictive power of IL-6[276, 297]. Certainly, from animal studies, there is the suggestion that trans-signalling is inhibited by administration of antibodies to sIL-6R[298]. There is the potential that some redundancy in the amount of sIL-6R available could account for this result. Alternatively, soluble gp130, which we did not measure in this study, may need to be factored in. We are not aware of any other research on preoperative IL-6 and POD that controlled for or explored interactions with sIL-6R or TNF-α. There are studies however on the association between sIL-6R and POD. In their study on older hip fracture surgery patients, Neerland et al did not find an association between preoperative sIL-6R and postoperative delirium[176]. Incidentally, preoperative IL-6 was also not significantly different between POD and no POD groups in that study. Conversely, Zhang et al found an association between postoperative sIL-6R and POD[295]. Unfortunately, although preoperative levels were measured, analysis for preoperative associations was not reported.

Regarding preoperative IGF-1, our systematic review did not reveal an association with POD. Similarly, our study findings did not support preoperative IGF-1 as a predictor of POD. To further explore this (a priori plan), the regression model was adjusted for IGFBP-3. A further regression model on the prediction of POD by the interaction of IGF-1 and IGFBP-3 was performed. Neither resulted in improved prediction of POD. The hypothesis that there may be an inverse relationship between IGF-1 and POD is not without merit given that IGF-1 is neuroprotective and has anti-inflammatory properties[73]. This may account for the availability of several studies on this, albeit with conflicting results. Unfortunately, none of the studies identified measured IGFBP-3. Given that this is the first study to our knowledge that explored interaction between IGF-1 and IGFBP-3 or adjusted IGF-1 for IGFBP-3 levels in the context of POD, more research is required to confirm or refute our findings.

The limitations of this study need to be acknowledged. As a hypothesis generating/supporting study of a design that is unique, the opportunity to conduct sample size calculations based on other studies of this kind was not available. As a result, a pragmatic sample size, guided by literature on pilot studies, of 45 -60 was decided. It is plausible that our sample size is not large enough to overcome type II error. That said, the study provides a first look at the prediction of POD by the trajectory and interactions of preselected inflammatory mediators. It also provides data that may inform sample size calculations in future studies. On the topic of sample size, this study was conducted during and 'after' the COVID-19 pandemic. The association of COVID-19 with cytokine storm is extensively documented[299]. Carefully screen of potential participants and exclusion people with COVID-19, significantly impacting the pool of patients to recruit from. Another limitation lies in the complex interactions between inflammatory mediators. Some have used an inflammation score (pro-inflammatory – anti-inflammatory mediators)[2, 186], however handling of pleiotropic cytokines such as IL-6 and TNFα is problematic. On the topic of interaction between IL-6 and TNFα, Il-6 derived from muscle cells has an inhibitory effect on TNF-α production[300]. In this study, we adjusted for some of the known interactions between inflammatory mediators. However, there are other modifiers that may need to be adjusted for in future studies e.g. soluble gp130.

Overall, raised IL-6, irrespective of its cause, may be a predictor of POD. However, given the moderate effect of IL-6, there must be other factors that act in concert with IL-6 for POD to occur.

The premise of this work is that summation of an individual's intrinsic vulnerabilities may breach a threshold resulting in POD. By identifying and quantifying the contribution of preoperative IL-6 to the incidence of POD, it is plausible that the understanding the proportional contributions of other intrinsic vulnerabilities is attainable.

Considering our findings, the proposed pseudo formula for POD, may be updated with preoperative IL-6 replacing cytokine dynamics and β1 a constant derived from the pseudo R^2 and cut-off value of preoperative IL-6 (proposed 42.86 pg/ml). In the same vein, the cytokine dynamics across surgery may be removed.

Risk of POD = β_0 + (β_1 x preoperative IL-6) + (β_3 x intrinsic brain vulnerability) + (β_4 x environmental factors) + Ɛ

Conclusion

In this cohort of older hip fracture patients, the trajectory of preselected inflammatory mediators did not predict the occurrence of POD. Preoperative IL-6 levels may be a fair predictor of POD. IGF-1 was not a predictor of POD despite adjustment for IGFBP levels. Larger, multicentre studies are required to confirm or refute this study's findings.

Concluding remarks, future directions and reflection chapter

Premise of thesis

Postoperative delirium provides a challenge given the diverse factors already associated with it. One approach to unravelling the aetiology of POD, or other acute mental disorders could be a search for a final common trigger[301] or overarching hypothesis[33].

With this work, we suggest POD is a 'threshold for dyshomeostasis' problem. By this we mean that the additive effect of anomalies in various domains of vulnerability may result in POD if a certain threshold is breached. To investigate our premise, measurable and easily accessible biomarkers of vulnerabilities in the different domains must be identified.

Prior to starting this project, biomarkers for intrinsic vulnerabilities in the domain of inflammation had been investigated by several researchers. However, while those efforts are applauded for the insights they provide, the results of these studies were unsatisfactory for a number of reasons discussed here. The conflicting results from different studies regarding the association between inflammatory mediators and POD proved problematic. The absence of a plausible reason for these differences in outcomes was also concerning especially in the context of declarations for or against the predictive role of these mediators and POD. On the topic of associations and predictions, it is my understanding that the efficacy of a biomarker is better quantified by its predictive estimate assessed by logistic regression analysis, especially since the outcome variable is categorical. The use of associations (assessed using Mann Whitney test, Student's T test, linear regression) in some inflammatory mediator studies makes the link between a positive association and risk prediction tenuous. Finally, the complex interactions between inflammatory mediators and other mediators, receptors or binding proteins appears to be rarely if at all considered. That said, prior research suggests that preoperative inflammatory status may play a role in prediction of POD.

Regarding biomarkers of intrinsic brain vulnerability, overt cognitive impairment i.e. MCI and dementia are widely recognised as risk factors for POD. However, there is a dearth of information or simple bedside tools for assessment of intrinsic brain vulnerability in overtly cognitively intact older people. While the utility of the abbreviated mental test score and mini mental state examination is appreciated, it must also be acknowledged that these tools were designed as screening tools for clinical cognitive impairment as opposed to preclinical neurodegeneration[302, 303]. Regarding preclinical neurodegeneration, there is ample evidence of brain MRI detection of regional atrophy associated with future dementia. However, for routine biomarker assessment in clinical practice, MRI is impractical for a variety of reasons.

In this work, we attempted to clarify the predictive efficacy of preselected inflammatory mediators on the occurrence of POD. We also set out to identify simple, cost-effective bedside tools that may be used to assess proposed biomarkers of intrinsic brain vulnerability.

In the run up to this work, our intent also included a study on functional and network MRI analysis of POD compared to no POD in overtly cognitively intact older people. In this study we planned to correlate the structural abnormalities with the DTI and functional connectivity changes using the dorsolateral prefrontal cortex and the hippocampus as the regions of interest. These areas were selected in view of their role in executive function and memory, both domains of cognition affected by POD. The salience network, was also a network of interest. The salience network is a large network believed to be implicated in directed attention[304]. In the resting state, the activity of the default mode network (previously described) is prominent. On assumption of an active state e.g. performing a task, the activity in the salience network and central executive network increases. The salience network is thought to act like a 'switch' from the default mode to the task focussed states[305, 306]. Damage to the salience network has been associated with abnormal cognitive responses in traumatic brain injured people[307], psychiatric conditions[308], and amnestic MCI/dementia[309]. The desire to explore the salience network in people with POD is therefore reasonable. A protocol was developed and approved by the research ethics committee. Unfortunately due to the COVID-19 pandemic and subsequent difficulties, this study has not yet occurred.

A summary of the results of our first steps in this journey are summarised below.

Summary of thesis

Systematic review of preoperative inflammatory mediators and POD

This systematic review was undertaken, mainly to clarify what was known, thus far, about associations between preoperative inflammatory mediators and postoperative delirium. Despite a reasonable number of studies on a wide variety of cytokines, preoperative IL-6 emerged as the cytokine associated with POD. However, most studies reported an association not causality which is problematic for individualised POD prediction[310]. Also, exploring other cytokines during this review raised questions, such as the impact of change in cytokines across surgery on POD. We were particularly piqued by the absence of an inverse association between IGF-1 and POD. A study protocol was therefore developed to begin to address these questions.

Systematic review optical coherence tomography and mild cognitive impairment

Intrinsic brain vulnerability, specifically preclinical neurodegeneration in overtly cognitively intact older people was proposed as a contributor to POD risk. However, to my knowledge, there are no easily accessible bedside tools to assess preclinical neurodegeneration. Our review of literature on factors associated with established dementia revealed retinal nerve fibre layer thickness as a potential candidate. The premise of this systematic review was to understand the literature on RNFL thickness measured using optical coherence tomography

in people with POD or MCI. The interest in MCI reflects our working trajectory of cognitively normal ➔ overtly cognitively normal with preclinical neurodegeneration ➔ MCI ➔ Dementia. Unfortunately, there were no published studies on RNFL and delirium of any aetiology hence the review was on MCI. This systematic review and meta-analysis demonstrated an association between thinning of the circumpapillary RNFL and MCI particularly amnestic MCI. The findings of this review informed the study protocol for RNFL thickness and POD.

Retinal fibre layer thickness and POD feasibility study

To my knowledge, this is the first study on RNFL thickness and POD. The initial plan for this study was to transfer participants to the ophthalmology department for retinal imaging. The logistic challenges this raised resulted in a search for a bedside alternative. A handheld OCT device was identified. This device was used and feasibility of acquiring useful images at the participants' bedside demonstrated. In this cohort of overtly cognitively intact older people recovering from hip fracture surgery, cpRNFL was thinner in the POD group despite the small number of participants in this feasibility study. However, we identified limited utility of this tool in the context of POD risk assessment, given the preponderance of modifiers of RNFL thickness in this age-group (51.6% of people presenting for hip fracture surgery during our study period had modifiers of RNFL thickness). That said, further exploration of RNFL thickness in POD is supported by the findings of this study.

Preoperative posterior dominant rhythm and POD

The search for measurable changes associated with overt cognitive impairment that may be present in covert neurodegeneration identified EEG as a potential candidate. The serendipitous, routine use of processed EEG during the conduct of anaesthesia, provided the opportunity to explore resting state posterior dominant rhythm (PDR) as a potential surrogate for intrinsic brain vulnerability. Feasibility of acquiring measurable, raw EEG signal using the Narcotrend monitor was demonstrated. However there was no significant difference between groups in the PDR between POD and no POD groups. This probably needs to be addressed in a future study powered for this outcome.

Inflammatory mediators and postoperative delirium – Trajectories, preoperative values and interactions

This work sought to answer some questions raised by the systematic review on preoperative inflammatory mediators and POD, particularly trajectories of inflammatory mediator, interactions between mediators and the role of IGF-1. Preoperative IL-6 was identified as a potential predictor of POD in overtly cognitively intact older people undergoing hip fracture surgery. The trajectory of IL-6 alone or adjusted for established modifiers (age, frailty, comorbidities and dexamethasone dose) and proposed modifiers (sIL-6R and TNFα) was not

predictive of POD. In addition, the trajectory of IGF-1 alone or adjusted for established modifiers and proposed modifiers (IGFBP-3) was not predictive of POD. Preoperative IGF-1 alone or adjusted for IGFBP levels was also not predictive of POD. The findings of this study will need to be validated in larger studies.

Limitations of this work

While this work has contributed to the ongoing study of biomarkers of POD, it has a few limitations.

Of note is the requirement to change direction and pause research activities during the COVID-19 pandemic. The pause in activity was to support the COVID-19 response of my Trust. As an anaesthetist, my clinical skills were required. In addition, COVID-19 had a significant impact on elective surgery, significantly curtailing the pool from which participants could be recruited. Furthermore, the high incidence of COVID-19 infection in older people further reduced my potential recruitment pool. The impact of this can be gleaned from the duration required to recruit participants in each of the studies.

The study protocols were developed and approvals obtained for study delivery at the Queen's Medical Centre, Nottingham. During the study, colorectal surgery was moved to Nottingham City Hospital (also a part of the same NHS Trust). This further restricted the pool of participants at QMC. It could be argued that a protocol amendment could accommodate this. Unfortunately, during that period QMC was my base hospital as an anaesthetics trainee. The logistics of recruiting and performing postoperative assessments of participants in Nottingham City hospital precluded applying for a protocol amendment.

This seamlessly links in to resources. As the investigator delivering most aspects of the studies, balancing recruitment and full time anaesthetic training post mandated that participant recruitment be convenience sampling. I hasten to thank Mr Ethan Beckford and Jennie Spendlove for helping with the processed EEG study and OCT study (respectively) when possible. For studies of this sort, the availability of dedicated research nurses or fellows may enhance recruitment rates.

The study of RNFL thickness and posterior EEG rhythm as potential biomarkers of intrinsic brain vulnerability in the context of POD, is largely uncharted territory. As a result the studies were feasibility in design. That said, the data from these studies will support sample size calculation for future studies.

Conclusion

Postoperative delirium may result from a breach in a threshold by the summation of intrinsic vulnerabilities in the domains of inflammation, brain vulnerability and environmental factors. This work demonstrated that preoperative IL-6 is a predictor of POD and may be used as a biomarker of the inflammation domain. The feasibility of using the handheld OCT device and the processed EEG device to measure the cpRNFL thickness and

posterior EEG power (respectively) was demonstrated. Finally there is the potential that cpRNFL and posterior EEG power may be candidates for future investigation as biomarkers of intrinsic brain vulnerability in overtly cognitively intact older people

Future directions

Given the findings of this initial foray into POD prediction, larger studies are required to better clarify the role of the variables identified in this work. Fortuitously this work provides some essential data required to estimate appropriate sample sizes for future studies.

Retinal nerve fibre layer thickness

Given that our study suggests thinning of the cpRNFL may be associated with POD, a study, powered for POD prediction by RNFL thickness in overtly cognitively intact older people, to confirm or refute our finding is required. This ideally would be a multicentre study to facilitate recruitment of an appropriate sample size and to engender some diversity in the participant population. The study would also include follow-up of participants for up to five years to assess for new diagnosis of cognitive impairment or dementia. This will afford us the opportunity to assess the impact of POD, stratified by cpRNFL thickness on future cognitive outcome.

To validate cpRNFL thickness as a biomarker of covert neurodegeneration, a subgroup analysis involving brain MRI would be performed. This would involve selection of a limited number of participants with the aim of correlating the cpRNFL thickness with MRI brain changes.

Processed EEG and POD

Our study proved feasibility of obtaining preoperative posterior EEG for analysis from routinely used processed EEG monitor. Although there was no significant difference in posterior eyes-closed and eyes-open powers between POD and no POD groups, our data suggests a trend. This supports the development of a future study, powered by the data in this study, to explore the ability to predict POD using the posterior EEG power in overtly cognitively intact older people. This is particularly exciting because the processed EEG monitor is routinely used during the conduct of anaesthesia and therefore readily available. We acknowledge the current limitation that the data has to be converted before analysis. However, if the posterior power is proven to be a biomarker of intrinsic vulnerability, there is ample opportunity to collaborate with device manufacturers regarding extension of the routinely accessed device output i.e. an intrinsic brain vulnerability index.

As with RNFL, validation of posterior EEG power as a biomarker of intrinsic brain vulnerability will require validation by a substudy involving MRI. The aim of the substudy

would be to correlate posterior EEG power with MRI changes in brain regions associated with future dementia in overtly cognitively intact older people.

Interaction of vulnerabilities

Our initial hypothesis, i.e. threshold of summated vulnerabilities, suggests that the phenotype of POD occurs when the summation of intrinsic vulnerabilities breaches a threshold. The threshold may be fixed but the relative contributions of each area of vulnerability may vary. To further develop this hypothesis, more research is required specifically focussed on the integration of these domains in each participant. While the immediate future direction is to further clarify predictive capability of our proposed biomarkers of intrinsic vulnerabilities, a later study is required to incorporate all the biomarkers. This latter study will examine the prediction of POD in overtly cognitively intact older people by the additive effect of biomarkers in different domains of intrinsic vulnerability. Given our experience of recruitment patterns and prevalence of exclusions this will need to be a multicentre study. In this study, an assessment of POD prediction by the interaction of a measure of preoperative inflammation (IL-6), and measure(s) of intrinsic vulnerability (retinal nerve fibre layer thickness and/or posterior EEG power) simultaneously in overtly cognitively intact older people undergoing surgery with a two - five year follow-up may prove instructive. The follow-up is to assess for deterioration in cognitive function in the longer term

Salience network

The inability to conduct the MRI study was particularly upsetting especially with regards to examination of dysfunction of the salience network as a potential cause of POD. However, to compensate for this, the processed EEG study was developed and delivered. That said, given that the ethics and non-commercial contract for this work are already approved, and my interest in the salience network as a thing, I intend to deliver this study in future.

Personal reflections

On the future of postoperative delirium

An important concept in research is impact. Reflecting on the impact of this and future work of this nature, I imagine over the next few years certain changes in the perception of POD will occur. Primarily, POD in older people may come to be recognised as a barometer of the brain's resilience to perioperative insult, i.e. an early warning (to use popular NHS parlance) symptom of intrinsic brain vulnerability.

It is my hope that with more research, quantification of the extent of this intrinsic brain vulnerability using simple bedside tools will be routine. The use of pEEG during usual anaesthesia affords us the opportunity, with improved knowledge of features of intrinsic

brain vulnerability, to update the algorithms such that an intrinsic brain vulnerability index is also displayed. This brain vulnerability index would be useful in predicting POD risk. More significantly, it may help early identification of people at risk of future cognitive impairment or dementia.

Given the increased attention that POD has experienced recently and the amount of research activity around POD, it is plausible to imagine that over the course of the next 10 years, the prediction and management of POD would have improved significantly.

Regarding prediction of POD, this work has suggested a pseudo-equation suggesting quantifiable variables that may play a role in POD aetiology.

Risk of POD = β0 + (β1 x preoperative IL-6) + (β3 x intrinsic brain vulnerability) + (β4 x environmental factors) + Ɛ

We have benchmarked IL-6 as a plausible biomarker of preoperative inflammatory status that is associated with POD. Currently, IL-6 is not routinely measured in the NHS. However, our experience with procalcitonin during the COVID-19 pandemic, for example, demonstrates that if applicability and validity are demonstrated, the barriers to adopting certain investigations into 'routine' clinical practice are surmountable. That said, more research is required to fine tune and validate the measures of intrinsic brain vulnerability and environmental factors. Admittedly, during the course of this work I have come to understand that the interactions between the different variables are not as simplistic as depicted in Figure 1.1. The interactions depicted in Figure 7.1 are more representative, yet likely still simplistic, demonstration of my evolving understanding of POD aetiology.

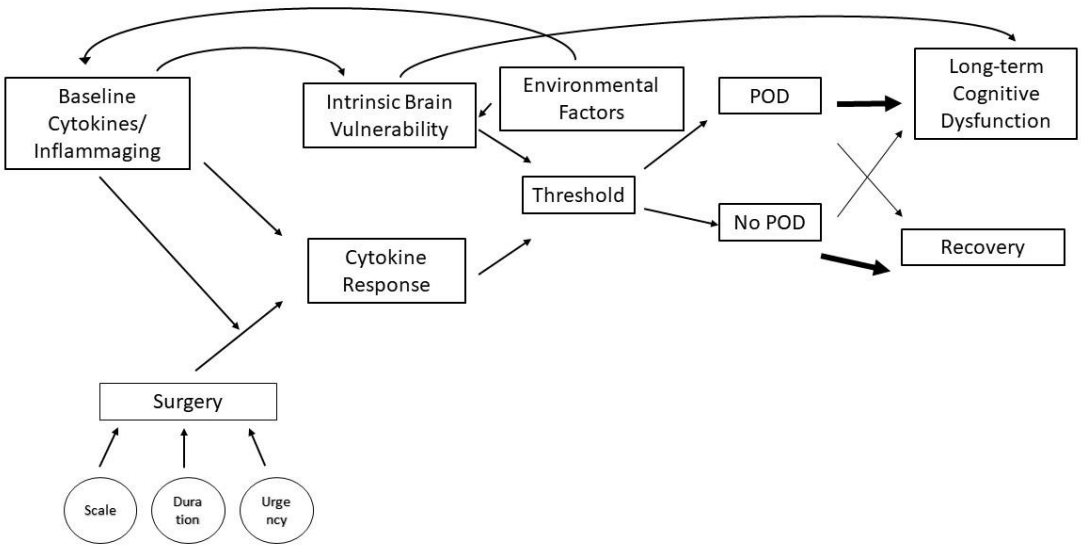

Figure 7.1: Updated path diagram demonstrating potential association between intrinsic vulnerabilities, POD and subsequent cognitive impairment.

The scenario I envisage for the future is an older person presenting for moderate or major surgery has a robust assessment of the variables discussed above to predict POD risk. The risk assessment will trigger the appropriate pathway for the individual patient's management. Pathways may include multicomponent non-pharmacological interventions, pharmacological interventions and improved management of staff and patient expectations. Given the role of preoperative IL-6 in the aetiology of POD, research into the use of preoperative modifiers of IL-6 levels is reasonable. A potential candidate is Tocilizumab which inhibits IL-6 by binding sIL-6R[311]. However, given Tocilizumab's side effect profile, careful investigation of the effect of a single dose of Tocilizumab preoperative in immunocompetent patients is required. Of equal importance, the patient's intrinsic brain vulnerability index could trigger a neurology review pathway.

On cognition

During this PhD, the importance of understanding the components of cognition, particularly memory has become clear to me. In the exploration of the predictors of POD, the recurring question that arises is 'what is cognition?' Particularly, what is memory? While there is an abundance of definitions and classifications of memory, e.g. semantic vs episodic or short-term vs long-term, the question about the true nature of memory remains[312]. Autobiographical memory, of relevance to POD and longer-term cognitive impairment, is also elegantly described[313]. However, the question persists. Is memory stored as a particle, or an energy field? Does it obey biological rules or is memory an energy/wave phenomenon – invoking quantum mechanics. There is certainly a premise for this line of thinking in consciousness research, e.g. Penrose-Hameroff's theory of orchestral objective reduction[314]. Asking and answering this question may go some way in enhancing our understanding and perhaps prevention of acute (i.e. delirium) and chronic cognitive impairment (MCI and dementia).

On COVID-19

The progress of this work was significantly impacted by the COVID-19 pandemic as was most clinical research across the world. Anecdotally, several research students turned their hand to COVID research or database data analysis. For a researcher focused on postoperative delirium, the COVID-19 pandemic highlighted the paucity of routinely collected data on postoperative delirium in clinical care. In the absence of retrospective data analysis, and given the clinical challenge of COVID-19, progress with the planned work was impeded. However, during the pandemic and pause in my academic activities, I had the opportunity to observe and document the experience of my colleagues (doctors, nurses, healthcare assistants, patient escort services etc.) who were delivering care on the frontline to COVID-

19 patients. The results of my observations (gathered using a survey) were presented to the people and culture committee of my NHS Trust and the findings disseminated amongst the relevant Heads of service.

On clinical research

Compared to before I started on this path, I am now even more convinced that clinical research is essential for improved patient outcomes. In all fairness, I believe this is evident to most clinicians. However, I am forced to admit that there are challenges along the way. Obtaining a grant, getting approvals, recruiting participants, subsequent withdrawals are but a few challenges that I experienced during this work. Despite these challenges, the potential opportunity to make a difference, to find something that takes us forwards, to contribute to the knowledge base, has thus far outweighed the burden of the challenges. An oft cited quote attributed to Horace Mann simply states “Be ashamed to die until you have won some victory for humanity”. I truly believe that clinical research provides us the opportunity to achieve this.

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Appendix

Appendix for systematic review on preoperative inflammatory mediators and POD

Search strategy for reviews on preoperative inflammatory mediators and postoperative delirium (POD)

Search for previous systematic reviews

Database of abstracts of reviews of effects (DARE)

Cytokines OR Inflammatory markers AND postoperative delirium - 0

Postoperative delirium – 11 (none relevant)

Cytokines AND delirium – 200 (none relevant)

PubMed Reviews

Postoperative delirium AND cytokines (All fields): 5 results (3 not relevant)

Postoperative delirium AND inflammatory markers: 3 results (2 not relevant)

Delirium AND Cytokines (All fields): 46 results (40 not relevant)

Cochrane database of systematic reviews

Postoperative delirium AND cytokine (all text); 2 results (none relevant)

Postoperative delirium AND inflammatory markers (all text); 5 results (none relevant)

Delirium AND Cytokine (all text): 12 results (none relevant)

Delirium AND Inflammatory markers (all text): 13 results (none relevant)

Postoperative delirium (Title, abstract, keyword): 10 results (none relevant)

Medline Reviews

Same keywords as for database search for articles (below) with meta-analysis selected: 9 results (8 not relevant)

Same keywords for database search for articles (below) with reviews selected: 20 results (17 not relevant)

Joanna Briggs Institute Database of Systematic reviews and Implementation Reports

Postoperative delirium – 26 (none relevant)

Delirium – 162 (none relevant)

Prospero International Prospective Register of Systematic Reviews

Postoperative delirium – 121 (none relevant)

Summary of identified pre-existing reviews of interest

- Surgery, neuroinflammation and cognitive impairment Alam A et al. eBioMedicine, November 2018: Narrative review.
- Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer's disease. Cortese GP et al. Behavioural brain research, March 2017: Narrative review.
- Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. Liu X et al. PloS one, April 2018: Systematic review and meta-analysis however was not exclusive to low risk of bias articles. Also did not separate out hip fracture studies, a cohort that already has the inflammatory system activated prior to admission.
- The immunology of delirium. Cerejeira J et al. Neuroimmunomodulation, February 2014. Narrative review.
- A systematic literature review of cerebrospinal fluid biomarkers in delirium. Hall RJ et al. Dementia and geriatric cognitive disorders, August 2011: Cerebrospinal fluid.
- The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review Simone MJ et al. CNS neuroscience & therapeutics, October 2011: Narrative review
- Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses MacLullich AM et al. Journal of psychosomatic research, September 2008: Narrative review.
- Serum biomarkers for delirium. Marcantonio ER et al. The journals of gerontology series A: Biological sciences and medical sciences, December 2006: Narrative review.
- Neural mechanisms of delirium: current hypotheses and evolving concepts. Flacker JM et al. Journals of gerontology series A: Biomedical sciences and medical sciences, June 1999: Narrative review.
- Biomarkers of delirium a review. Khan BA et al. Journal of the American Geriatrics Society, November 2011: Narrative review included IL-6, IL-8 and IGF-1. Only included studies with a sample size of 50 or greater.
- Pre-operative biomarkers and imaging tests as predictors of post-operative delirium in non-cardiac surgical patients: a systematic review. Ayob F et al. BMC anesthesiology, December 2019: Limited number of studies included hence no meta-analysis.
- Biomarkers and postoperative cognitive function: could it be that easy? Schaefer ST et al. Current opinions in anaesthesiology, February 2019: Literature search limited to January 1 2016 – 17 July 2018.

Search strategy for articles on preoperative inflammatory mediators and POD

Keywords

Delirium

Delirium, acute confusion, acute confusional state, acute organic psychosyndrome, acute brain syndrome, acute brain dysfunction, acute brain failure, metabolic encephalopathy, exogenous psychosis, toxic psychosis, toxic confusion

Surgery

Surgery, operation, postoperative, post-operative, perioperative, peri-operative, surgical

Postoperative delirium

Postoperative delirium, POD, postoperative cognitive dysfunction, POCD

Inflammatory markers

Cytokines, inflammatory markers, interleukin, insulin-like growth factor, tumour necrosis factor, interleukin 6, interleukin-6, c reactive protein, c-reactive protein, CRP, cortisol, Neopterin

Search strategy

Medline

Search terms for delirium

Delirium as Keyword and mapped: 19175

Acute confusion as keyword and mapped to cognition disorders: 65009

Acute confusional state as keyword phrase and mapped to confusion: 5120

Acute organic psychosyndrome as keyword phrase: 5

Acute brain syndrome as keyword: 44

Acute brain dysfunction as keyword: 111

Acute brain failure as keyword: 27

Metabolic encephalopathy as keyword and mapped to Brain diseases, Metabolic: 2420

Acute encephalopathy as keyword: 1260

Acute psychosis as keyword: 1145

Exogenous psychosis as keyword: 35

Toxic psychosis as keyword and mapped to delirium: 9801

Toxic confusion as keyword: 6

Summary of terms for Delirium: 91846

Search terms for surgery

Surgery as keyword or mapped to General surgery: 2705083

Operation as keyword and mapped to postoperative complications: 679955

Postoperative as keyword and mapped to postoperative care, postoperative complications and postoperative period: 817684

Post-operative as keyword: 63724

Perioperative as keyword and mapped to perioperative care and perioperative period: 110167

Peri-operative as keyword: 7185

Surgical as keyword: 1388347

Summary of terms for surgery: 3423311

Summary of all terms Surgery AND all terms Delirium: 9293

Search terms for POD

Post-operative delirium as keyword: 1742

POD as keyword: 16347

Postoperative cognitive dysfunction as keyword: 1165

POCD: 861

All Surgery AND All delirium: 9293

Summary of terms for POD: 25938

Search terms for inflammatory markers

Cytokines as keyword and mapped: 306152

Inflammatory markers as keyword: 21101

Interleukin as keywords and mapped to interleukins: 359973

Insulin-like growth factor as keyword and mapped to somatomedins: 61375

Tumour necrosis factor and mapped to tumour necrosis factor alpha: 136673

Interleukin 6 as keyword and mapped to interleukin 6: 91086

Interleukin-6 as keyword and mapped to interleukin-6: 91086

C reactive protein as keyword and mapped to C-reactive protein: 83865

C-Reactive protein and mapped to C-Reactive protein: 83865

CRP as keyword: 50923

Cortisol as keyword and mapped to Hydrocortisone: 95573

Neopterin as keyword and mapped to Neopterin: 3608

Summary of terms for inflammatory markers: 542066

Search terms for biomarkers

Biomarkers as keyword and mapped to biomarkers: 548125

Summary of terms for inflammatory markers OR biomarkers: 1318591

Search for POD AND inflammatory markers/biomarkers

Combination of POD and inflammatory markers/biomarkers using AND: 1766

PubMed

Search terms for POD

Post-operative delirium OR POD OR post-operative cognitive dysfunction OR POCD: 18746

Search terms for delirium

Delirium OR acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain failure OR acute brain dysfunction OR metabolic encephalopathy OR acute encephalopathy OR encephalopathy OR acute psychosis OR toxic psychosis OR toxic confusion OR exogenous psychosis: 238063

Search term for surgery

Surgery OR operation OR postoperative OR post-operative OR perioperative OR peri-operative OR surgical: 5778151

Combination of surgery and delirium using AND: 47174

Combination of all postoperative delirium terms: 64433

Search terms for inflammatory markers

Cytokines OR inflammatory markers OR Interleukin OR Insulin-like growth factor OR tumour necrosis factor OR interleukin 6 OR interleukin-6 OR C reactive protein OR C-reactive protein OR cortisol OR Neopterin: 1206227

Search for POD AND inflammatory markers

Combination of POD and inflammatory markers with AND: 3189

Embase

Search terms for delirium

Delirium as Keyword and mapped: 36670

Acute confusion as keyword and mapped: 951

Acute confusional state as keyword phrase and mapped to confusion: 30927

Acute organic psychosyndrome as keyword phrase and mapped to organic psychosyndrome: 919

Acute brain syndrome as keyword: 55

Acute brain dysfunction as keyword: 186

Acute brain failure as keyword: 40

Metabolic encephalopathy and mapped to metabolic encephalopathy: 2112

Acute encephalopathy as keyword and mapped to acute brain disease: 2510

Acute psychosis as keyword and mapped: 2642

Exogenous psychosis as keyword: 47

Toxic psychosis as keyword: 159

Toxic confusion as keyword: 10

Summary of terms for Delirium: 72813

Search terms for surgery

Surgery as keyword and mapped to surgery: 3656832

Operation as keyword and mapped to surgery: 1076043

Postoperative as keyword and mapped to postoperative delirium: 1055513

Post-operative as keyword and mapped to postoperative complication: 442263

Perioperative as keyword and mapped to perioperative period: 165038

Peri-operative as keyword: 15527

Surgical as keyword and mapped to surgical patient: 1719910

Summary of terms for surgery: 4460909

Summary of all terms delirium AND all terms surgery: 16338

Search terms for POD

Post-operative delirium as keyword and mapped: 3435

POD as keyword: 18845

Postoperative cognitive dysfunction as keyword and mapped: 2044

POCD: 1223

Surgery as keyword and mapped AND All delirium: 10357

Summary of terms for POD: 23738

All search terms POD OR (Surgery AND delirium): 36411

Search terms for inflammatory markers

Cytokines as keyword and mapped to cytokine: 444795

Inflammatory markers as keyword: 36687

Interleukin as keywords and mapped to interleukins: 727698

Insulin-like growth factor as keyword and mapped to somatomedins: 62603

Tumour necrosis factor and mapped: 170267

Interleukin 6 as keyword and mapped to interleukin 6: 268574

Interleukin-6 as keyword: 268574

C reactive protein as keyword and mapped to C reactive protein: 196069

C-reactive protein as keyword: 196069

CRP as keyword: 102102

Cortisol as keyword and mapped to hydrocortisone: 144659

Neopterin as keyword and mapped to neopterin: 5725

Summary of terms for inflammatory markers: 1355946

Search terms for Biomarkers

Biomarker as keyword and mapped to biological markers: 431963

Summary of biomarkers or inflammatory markers: 1718540

Search for POD AND inflammatory markers/biomarkers

Combination of POD and inflammatory markers/biomarkers using AND: 1368.

Scopus

Search terms for delirium

Delirium OR acute confusion OR acute confusional state OR Acute organic psychosyndrome OR acute brain syndrome OR acute brain failure OR acute brain dysfunction OR metabolic encephalopathy OR acute encephalopathy OR encephalopathy OR acute psychosis OR exogenous psychosis OR toxic psychosis Or toxic confusion: 811555

Search terms for surgery

Surgery OR operation OR perioperative OR peri-operative OR postoperative OR post-operative OR surgical: 11319667

All delirium AND all surgery: 277511

Search terms for POD

Postoperative delirium OR postoperative cognitive dysfunction OR POD OR POCD: 176064

All POD: 428595

Search terms for inflammatory markers

Cytokines OR inflammatory markers OR interleukin OR insulin like growth factor OR tumour necrosis factor OR interleukin 6 OR interleukin-6 OR c reactive protein OR C-reactive protein OR CRP OR Cortisol OR neopterin: 3417948

Biomarkers: 1419966

Biomarkers and Inflammatory markers combined with OR: 4319797

Search for POD AND inflammatory markers

Combination of POD and inflammatory markers/biomarkers using AND: 126890

Excluding environmental science, book chapter, book, short survey, note, retracted, nonhuman, animals, book series, conference proceedings, trade journal, book, arts and humanities, business, etc.: 350

CINAHL

Search terms for delirium

Delirium OR acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain failure OR acute brain dysfunction OR metabolic encephalopathy OR acute encephalopathy OR acute psychosis OR toxic psychosis OR toxic confusion OR exogenous psychosis: 21297

Search terms for surgery

Surgery OR operation OR perioperative OR peri-operative OR postoperative OR post operative OR post-operative OR post-surgical OR post-surgery OR surgical: 1207232

All delirium AND all surgery: 8356

Search terms for postoperative delirium

Postoperative delirium OR postoperative cognitive dysfunction OR POD OR POCD: 6923

All postoperative delirium: 13626

Search terms for inflammatory markers

Cytokines OR inflammatory markers OR interleukin OR insulin like growth factor OR tumor necrosis factor OR interleukin 6 OR interleukin-6 OR c reactive protein OR C-reactive protein OR CRP OR Cortisol OR neopterin: 139263

Biomarkers: 76531

Biomarkers OR inflammatory markers: 200851

Search for POD AND inflammatory markers/biomarkers

Combination of POD and inflammatory markers/Biomarkers using AND: 2264

Limited to academic journals: 2168

Cochrane

Search terms for delirium

Delirium OR acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain failure OR acute brain dysfunction OR metabolic encephalopathy OR acute encephalopathy OR acute psychosis OR toxic psychosis OR toxic confusion OR exogenous psychosis: 8749

Search terms for surgery

Surgery OR operation OR perioperative OR peri-operative OR postoperative OR post-operative OR surgical: 301440

All delirium AND all surgery: 3232

Search terms for POD

Post-operative delirium OR POD OR postoperative cognitive dysfunction OR POCD: 4444

Summary of terms for POD: 5846

Search terms for inflammatory markers

Cytokines OR inflammatory markers OR interleukin OR insulin like growth factor OR tumour necrosis factor OR interleukin 6 OR interleukin-6 OR c reactive protein OR C-reactive protein OR CRP OR Cortisol OR neopterin: 68349

Search for POD AND inflammatory markers

POD AND inflammatory markers: 644 (389 trials)

Web of Science

Search terms for delirium

Delirium OR acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain failure OR acute brain dysfunction OR metabolic encephalopathy OR Acute encephalopathy OR acute psychosis OR toxic psychosis OR toxic confusion OR exogenous psychosis: 60500

Search terms for surgery

Surgery OR operation OR perioperative OR peri-operative OR postoperative OR post operative OR surgical: 4920980

Search terms for POD

Post-operative delirium OR POD OR postoperative cognitive dysfunction OR POCD: 47503

Surgery AND All delirium: 11846

Summary of terms for POD: 55170

Search terms for inflammatory markers

Cytokines OR inflammatory markers OR interleukin OR insulin like growth factor OR tumour necrosis factor OR interleukin 6 OR interleukin-6 OR c reactive protein OR C-reactive protein OR CRP OR Cortisol OR neopterin: 924819

Search for POD and inflammation

POD AND inflammatory markers: 1907

PsycInfo

Search terms for delirium

Delirium as Keyword and mapped: 7288
Acute confusion as keyword and mapped to mental confusion and delirium: 4449
Acute confusional state as keyword phrase: 139
Acute organic psychosyndrome as keyword phrase: 2
Acute brain syndrome as keyword: 35
Acute brain dysfunction as keyword: 21
Acute brain failure as keyword: 14
Metabolic encephalopathy as keyword and mapped to encephalopathies: 5012
Acute encephalopathy as keyword: 203

Acute psychosis as keyword and mapped: 2598
Exogenous psychosis as keyword: 20
Toxic psychosis as keyword and mapped to toxic psychoses: 272
Toxic confusion as keyword: 2
Summary of terms for Delirium: 16050

Search terms for surgery
Surgery as keyword or mapped to surgery: 86650
Operation as keyword: 25989
Postoperative as keyword and mapped to postsurgical complications: 8215
Post-operative as keyword and mapped to surgical patients: 4656
Perioperative as keyword: 1094
Peri-operative as keyword: 96
Surgical as keyword: 21849
Summary of terms for surgery: 122094

Summary of all terms Surgery AND all terms Delirium: 1394

Search terms for POD
Post-operative delirium as keyword: 32
Postoperative delirium as keyword: 320
POD as keyword: 434
Postoperative cognitive dysfunction as keyword: 147
POCD: 145
Summary of terms for POD: 1919

Search terms for inflammatory markers
Cytokines as keyword and mapped: 14650
Inflammatory markers as keyword and mapped to neuroinflammation: 5603
Interleukin as keywords and mapped to interleukins: 7979
Insulin-like growth factor as keyword and mapped: 1206
Tumour necrosis factor and mapped to tumor necrosis factor: 1843
Interleukin 6 as keyword: 3482
Interleukin-6 as keyword: 3482
C reactive protein as keyword: 3042
C-Reactive protein as keyword: 3042
CRP as keyword: 2186
Cortisol as keyword and mapped to Hydrocortisone: 16795
Neopterin as keyword: 237
Summary of terms for inflammatory markers: 39458

Search terms for Biomarkers
Biomarkers as keyword and mapped to biological markers: 26065
Summary of terms for inflammatory markers OR biomarkers: 61796

Search for POD AND inflammatory markers/Biomarkers
Combination of POD and inflammatory markers/biomarkers using AND: 171

All databases articles only - 9514

Risk of bias for all studies irrespective of RoB assessment

Data items for preoperative inflammatory mediators and POD systematic review

Article characteristics

Article title, author, source, year of publication, reason for inclusion, marker measured, timing of marker measurement, country of study, language, abstract, article type, study type, number of centres.

Participant recruitment criteria, baseline and interventions

Surgical type, urgency, inclusion criteria, exclusion criteria, participant sampling method, dementia included or excluded, dementia screening used, diagnostic criteria for delirium, diagnostic tool for delirium, timing of delirium assessments, personnel performing delirium assessment, incidence of delirium, screening for prevalent delirium

Delirium outcomes

Number of participants, mean age of participants, number with incident delirium, mean age of participants with incident delirium, number without delirium, mean age of participants without delirium, male to female ratio.

Blood Processing

Blood component assayed (serum/plasma), assay method, Actual factor measured, brand of assay kit, inter-assay coefficient of variation, detection levels, values below detection levels, handling of values below detection level, timing of preoperative blood sample.

Inflammatory mediators assayed preoperatively

Measured levels of markers

Statistical analysis and confounders

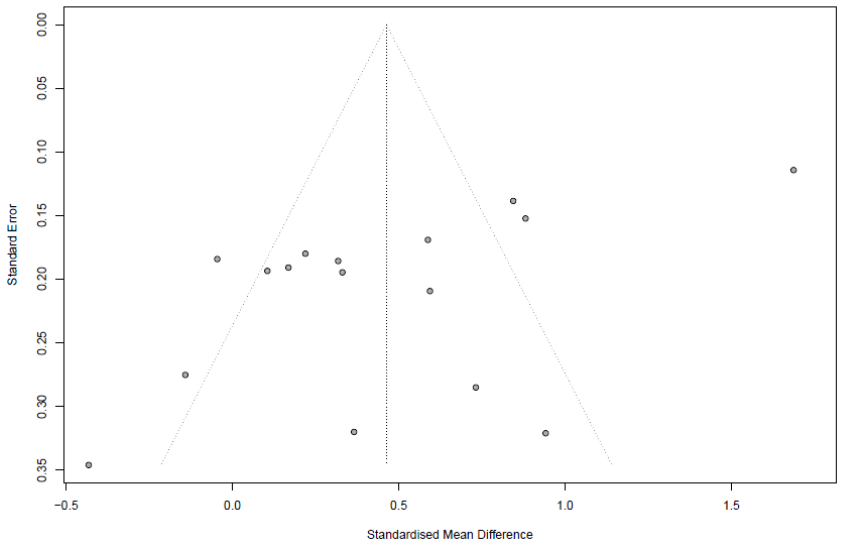
Statistical methods, adjustment for confounders

Differences in confounders between groups e.g. age, sex, dementia status, level of education, comorbidities, mini mental state examination, and ASA status.

Other

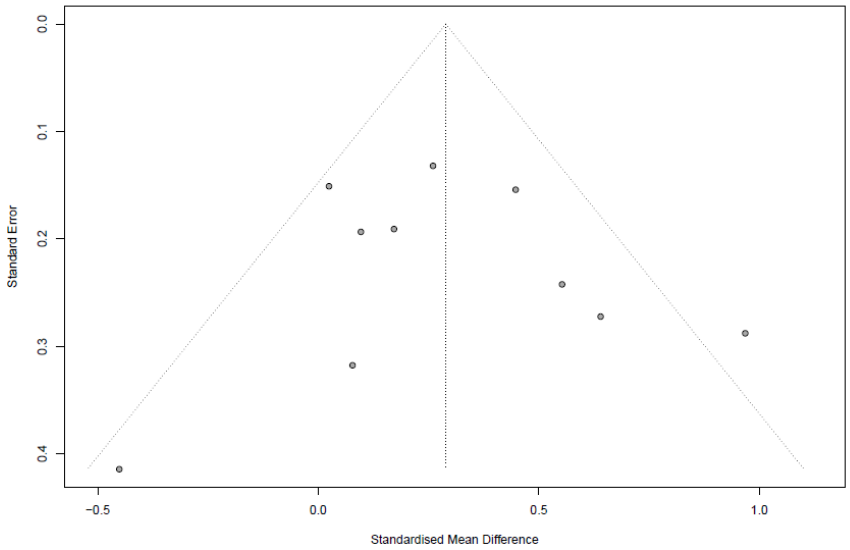
Authors' comments

Funnel plot for all studies (irrespective of risk of bias analysis) on preoperative C-reactive protein and postoperative delirium



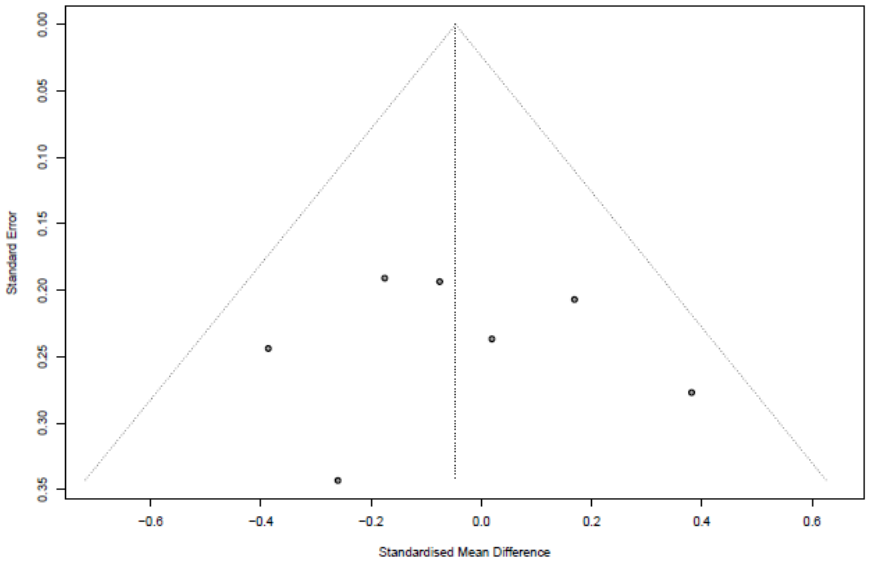
Funnel plot of 16 studies on preoperative C-reactive protein and postoperative delirium

Funnel plot for all studies (irrespective of risk of bias analysis) on preoperative interleukin-6 and postoperative delirium



Funnel plot of ten studies on preoperative interleukin-6 and postoperative delirium

Funnel plot for all studies (irrespective of risk of bias analysis) on preoperative insulin-like growth factor-1 and postoperative delirium



Funnel plot of seven studies on preoperative insulin-like growth factor-1 and postoperative delirium.

Appendix for systematic review on optical coherence tomography and MCI/delirium

Search strategy for reviews on optical coherence tomography and MCI/delirium

Database of abstracts of reviews of effects (DARE)

Search Terms: OCT OR Optical Coherence Tomography (1991 – 2019): 39 'hits': - No relevant systematic reviews

Search Terms: Delirium AND Optical Coherence Tomography (1991 – 2019): - No systematic reviews

Search Terms (1991 – 2019): Mild cognitive Impairment AND Optical Coherence Tomography: - No systematic reviews

Search Terms (1991 – 2019): Delirium AND retinal Nerve Fiber Layer: - No systematic reviews

Search Terms: Mild cognitive Impairment AND Retinal Nerve Fiber Layer (1991 – 2019): - No systematic reviews

Search terms: Delirium AND Ganglion cell (1991 – 2019): - No systematic reviews

Search terms (1991 – 2019): Mild cognitive Impairment AND Ganglion cell: - No systematic reviews

Search Terms: - Delirium AND Retinal Pigmented Epithelium: - No Systematic reviews

Search Terms: - Mild cognitive impairment AND Retinal Pigmented Epithelium: - No Systematic Reviews

Cochrane database of systematic reviews

Search Terms: Optical coherence tomography OR OCT scan AND Mild Cognitive Impairment: - 5 Systematic Reviews – No relevant

Search Terms: Optical coherence tomography OR OCT scan AND delirium: 5 Systematic reviews (same as above) – No relevant

Search terms: Optical coherence Tomography OR Retinal Nerve Fiber Layer AND delirium: - 10 Systematic reviews – No relevant

Search terms: Optical Coherence tomography OR Retinal Nerve Fiber Layer AND Mild cognitive impairment: 10 systematic reviews – No relevant

Search Terms: Optical coherence tomography OR retinal Nerve Fiber Layer AND cognitive Dysfunction (MESH): - 10 systematic Reviews – No relevant

Search Term Optical Coherence Tomography OR Ganglion cell layer AND delirium: - 2 systematic reviews – No relevant

Search terms: Optical coherence tomography OR Ganglion Cell Layer AND cognitive Dysfunction: - 2 systematic reviews – No relevant

Search Terms: - Optical coherence Tomography OR Retinal Pigmented Epithelium AND Delirium: - 34 Systematic reviews – No relevant

Search terms: - Optical Coherence Tomography OR Retinal Pigmented Epithelium AND Mild cognitive impairment: - 34 Systematic Reviews – No relevant

PubMed Reviews

Search terms: (Optical coherence tomography OR SDOCT OR retinal Nerve Fiber Layer OR Retinal Nerve Fibre Layer OR Ganglion cell Layer OR Ganglion cell inner plexiform layer OR GC-IPL OR Retinal pigmented epithelium) AND (Delirium OR acute confusion OR Acute confusional state): - No systematic reviews

Search Terms: (Optical coherence tomography OR SDOCT OR retinal Nerve Fiber Layer OR Retinal Nerve Fibre Layer OR Ganglion cell Layer OR Ganglion cell inner plexiform layer OR GC-IPL OR Retinal pigmented epithelium) AND (Mild Cognitive Impairment OR Cognitive Dysfunction): - 12 Systematic Reviews. (Parkinson's Disease – 2, General Neurologic Disease – 3, Alzheimer's disease – 1, Absent Search Methodology – 2 (Both narratives), Retinal Nerve fiber layer only – 2, All layers but limited search engines and 1, Not relevant – 1).

Medline Reviews

Search Terms: (Optical coherence tomography OR SDOCT OR retinal Nerve Fiber Layer OR Retinal Nerve Fibre Layer OR Ganglion cell Layer OR Retinal Ganglion Cell OR Ganglion cell inner plexiform layer OR GC-IPL OR Retinal pigmented epithelium OR Retinal Pigment Epithelium) AND (Delirium OR acute confusion OR Acute confusional state): - No systematic reviews

Search Terms: (Optical coherence tomography OR SDOCT OR retinal Nerve Fiber Layer OR Retinal Nerve Fibre Layer OR Ganglion cell Layer OR Retinal Ganglion Cell OR Ganglion cell inner plexiform layer OR GC-IPL OR Retinal pigmented epithelium OR Retinal Pigment Epithelium) AND (Mild cognitive impairment OR Mild cognitive dysfunction OR MCI OR Cognitive dysfunction OR cognition disorders): - 7 systematic Reviews. (Not relevant – 4, Absent search strategy and narrative review – 1, General – 1, Alzheimer's Disease – 1)

Nice Evidence

Search Term: Optical coherence tomography: - 77 systematic reviews. – 2 relevant (RNFL - 1 Scholar and PubMed, All layers – 1 EMBASE and PubMed)

Search Term: Retinal Nerve Fiber Layer: - 16 systematic reviews. No relevant.

Search Term: Ganglion Cell Inner Plexiform Layer: - 3 Systematic reviews. 1 relevant (All layer PubMed EMBASE)

Search Term: Retinal Pigmented Epithelium: - 2 Systematic reviews. No relevant

Joanna Briggs Institute Database of Systematic reviews and Implementation Reports

Search Term: Optical coherence Tomography: - 77 Articles. No relevant

Search Terms: (Optical Coherence tomography OR OCT OR SDOCT OR Retinal Nerve Fiber layer OR Retinal Nerve Fibre Layer OR Retinal Pigmented Epithelium OR Ganglion Cell Inner Plexiform Layer) AND (Delirium OR Acute Confusion OR Acute Confusional State): - 11 Systematic reviews. No relevant

Search Terms: (Optical Coherence tomography OR OCT OR SDOCT OR Retinal Nerve Fiber layer OR Retinal Nerve Fibre Layer OR Retinal Pigmented Epithelium OR Ganglion Cell Inner Plexiform Layer) AND (Mild cognitive Impairment OR Mild Cognitive Failure OR Mild Cognitive Dysfunction OR MCI Or Mild Cogni*): - 3 Systematic Reviews. No relevant.

Prospero International Prospective Register of Systematic Reviews

Search Terms: Optical coherence tomography:- 39 records. 1 on OCT and MCI stage of Alzheimer's disease

Summary of identified reviews of interest

- Spectral-domain OCT measurements in Alzheimer's disease: a systematic review and meta-analysis. Chan VT et al. Ophthalmology. 2019 Apr 1;126(4):497-510: Systematic review and meta-analysis. Two databases, AD and MCI, six studies on MCI and cpRNFL with 305 MCI cases, included studies on cognitive impairment no dementia (CIND) in MCI group. No significant difference in RNFL thickness between MCI and controls.
- A systematic review and meta-analysis of retinal nerve fiber layer change in dementia, using optical coherence tomography. Thompson KL et al. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2015 Jun 1;1(2):136-43: Systematic review and meta-analysis. RNFL in AD and MCI. Two databases. Five studies on MCI with 214 MCI cases. RNFL significantly thinner in MCI cases vs controls.
- Retinal nerve fiber layer thickness in amnestic mild cognitive impairment: Case-control study and meta-analysis. Knoll B et al. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2016 Jan 1;4:85-93: Combination of case-controls

study and meta-analysis. RNFL and MCI. Six databases. Six studies with 161 MCI cases. RNFL thickness significantly lower in MCI.

- Meta-analysis of the relationship of peripheral retinal nerve fiber layer thickness to Alzheimer's disease and mild cognitive impairment. Meijuan WA et al. Shanghai archives of psychiatry. 2015 Oct;27(5):263: Systematic review and meta-analysis. RNFL in AD and MCI. Ten databases. Nine studies with 252 MCI cases (four of these were low quality by the authors' assessment). RNFL thinner in MCI compared to controls.
- Retinal thickness in Alzheimer's disease: a systematic review and meta-analysis. Den Haan J et al. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2017 Jan 1;6:162-70: Systematic review and meta-analysis. AD and MCI. Two databases. Eight studies on RNFL and MCI with 216 MCI cases. RNFL in MCI thinner than healthy controls and thicker than AD.
- The role of optical coherence tomography in Alzheimer's disease. Cunha LP et al. International journal of retina and vitreous. 2016 Dec;2(1):1-1: Narrative review. Largely focussed on AD.
- Optical coherence tomography in Alzheimer's disease: a meta-analysis. Coppola G et al. PloS one. 2015 Aug 7;10(8):e0134750: Systematic review and meta-analysis RNFL in AD and MCI. Two databases. Three studies on RNFL in MCI vs controls. RNFL thinner in MCI vs controls.

Search strategy for articles on optical coherence tomography and MCI

Keywords

Mild Cognitive Impairment (MCI)

Mild cognitive impairment, mild cognitive dysfunction, mild cognitive failure, MCI, amnestic MCI, amnestic mild cognitive impairment, mild dementia.

(The search term mild dementia was included to allow for variable interpretation of mild dementia).

Optical Coherence Tomography (OCT)

Optical coherence tomography, OCT, SDOCT, SD-OCT, retinal nerve fiber layer, retinal nerve fibre layer, RNFL, nerve fiber layer, nerve fibre layer, ganglion cell layer, ganglion cell inner plexiform layer, GCIPL, retinal pigmented epithelium, retinal pigment epithelium, RPE.

Results were then combined using AND as the Boolean operator i.e.

Search results for all terms for mild cognitive impairment AND search results for all terms for optical coherence tomography.

Search strategy

Medline

Search Terms for MCI

Mild cognitive impairment (Keyword.) and Cognitive dysfunction (mapped subject heading): - 16551

Mild cognitive dysfunction (Keyword.) and Cognition disorders (mapped subject heading): - 55010

Mild cognitive failure (Keyword.): - 1

MCI (Keyword.): - 10648

Amnestic MCI (Keyword.): - 653

Amnestic mild cognitive impairment (Keyword.): -1371

Mild dementia (Keyword.): - 798

Summary of terms for MCI (using OR): - 71704

Search Terms for OCT

Optical coherence tomography (Keyword) and Tomography, Optical coherence (mapped subject heading): - 30886

OCT (Keyword.): - 22543

SDOCT (Keyword.): - 212

SD-OCT (Keyword.): - 2727

Retinal nerve fiber layer (Keyword.): - 3297

Retinal nerve fibre layer (Keyword.): - 680

Nerve fiber layer (Keyword.): - 4005

Nerve fibre layer (Keyword.); - 807

Ganglion cell layer (Keyword.) and Retinal ganglion cells (mapped subject heading): - 11967

Ganglion cell inner plexiform layer (Keyword.): - 235

GCIPL (Keyword.): - 145

Retinal pigmented epithelium (Keyword.) and Retinal pigment epithelium (mapped subject heading) and Pigment epithelium of eye (mapped subject heading): - 9988

RPE (Keyword.): - 9605

Summary of terms for OCT (using OR): - 60653

OCT AND MCI: - 84 documents (17 potentially relevant documents).

Search Terms Delirium

Delirium (kw.) and Delirium (MESH): - 9973

Acute Confusion (kw.): - 261

Acute confusional state (kw.) and Confusion (MESH): -2856

Acute organic psychosyndrome (kw.): - 0

Acute brain syndrome (kw.): - 10

Acute brain dysfunction (kw.): - 61

Acute brain failure (kw.): - 11

Metabolic encephalopathy (kw.) and Brain disease, Metabolic (MESH): - 1248

Acute psychoorganic syndrome (kw.): - 0

Clouded state (kw.): - 0

Clouding of consciousness (kw.): - 81

Exogenous psychosis (kw.): - 10

Toxic psychosis (kw.): - 22

Toxic confusion (kw.) and neurotoxicity syndromes (MESH): - 4622

Obnubilate (kw.): - 0

Obnubilat* (kw.): - 1

Summary of terms for delirium (using OR): -18444

OCT AND Delirium: - 19 documents (No relevant documents)

EMBASE

Search Terms MCI

Mild cognitive impairment (kw.) and (MESH) and cognitive defect (MESH): - 166282

Mild cognitive dysfunction (kw.): - 191

Mild cognitive failure (kw.): - 1

MCI (kw.): - 28652

Amnestic MCI (kw.): - 1496

Amnestic mild cognitive impairment (kw.): - 2598

Mild dementia (kw.): - 1729

Summary of terms for MCI (using OR): - 180682

Search Terms OCT

Optical coherence tomography (kw) and Optical coherence tomography (MESH): - 53927

OCT (kw) and spectral domain optical coherence tomography (MESH): - 54348

SDOCT (kw.) and Retinal thickness (MESH): - 3898

SD-OCT (kw.): - 5498

Retinal nerve fiber layer (kw.) and (MESH): - 7265

Retinal nerve fibre layer (kw.): - 1291

RNFL (kw.) and retinal nerve fiber layer thickness (MESH): - 6553

Nerve fiber layer (kw.) and retina neuroepithelial layer (MESH): - 9616

Nerve fibre layer (kw.): - 1533

Ganglion cell layer (kw.) and retina ganglion cell (MESH): - 18397

Ganglion cell inner plexiform layer (kw.): - 468

GCIPL (kw.): - 306

Retinal pigmented epithelium (kw.) and retinal pigment epithelium (MESH): - 4816

RPE (kw.): - 16881

Summary of terms for OCT (using OR): - 112160

OCT AND MCI: - 420 Documents (42 potentially relevant documents).

Search Terms Delirium

Delirium (kw.) And (MESH) and postoperative delirium (MESH): - 29869

Acute Confusion (kw.) and (MESH) and confusion (MESH): - 27909

Acute confusional state (kw.): - 600

Acute organic psychosis syndrome (kw.): - 2

Acute brain syndrome (kw.) and acute brain disease (MESH): - 1293

Acute brain dysfunction (kw.): - 146

Acute brain failure (kw.): - 29

Metabolic encephalopathy (kw.) and (MESH): - 1798

Acute psychoorganic syndrome (kw.): - 1

Clouded state (kw.): - 1

Clouding of consciousness (kw.): - 235

Exogenous psychosis (kw.): - 36

Toxic psychosis (kw.): - 120

Toxic confusion (kw.): - 10

Obnubilate (kw.): - 0

Obnubilat* (kw.): - 3

Summary of terms delirium (using OR): - 58365

OCT AND delirium: - 51 Documents (No relevant documents)

PubMed

Search Terms OCT

Optical coherence tomography OR OCT OR SDOCT OR SD-OCT OR Retinal nerve fiber layer OR retinal nerve fibre layer OR nerve fiber layer OR nerve fibre layer OR Ganglion cell layer OR ganglion cell inner plexiform layer OR GCIPL OR retinal pigmented epithelium OR retinal pigment epithelium OR RPE: - 5212017

Search Terms MCI

Mild cognitive impairment OR mild cognitive failure OR Mild cognitive dysfunction OR MCI OR amnestic MCI OR Amnestic mild cognitive impairment OR mild dementia: - 62446

OCT AND MCI: - 4682 (26 potentially relevant documents).

Search Terms Delirium

Delirium OR Acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain dysfunction OR acute brain failure OR metabolic encephalopathy OR acute psychoorganic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR Toxic psychosis OR Toxic confusion OR obnubilate OR obnubilation: - 128648

OCT AND Delirium: - 9208 documents (No relevant documents)

Scopus

Search term OCT

Optical coherence tomography OR OCT OR SDOCT OR SD-OCT OR Retinal nerve fiber layer OR retinal nerve fibre layer OR nerve fiber layer OR nerve fibre layer OR Ganglion cell layer OR ganglion cell inner plexiform layer OR GCIPL OR retinal pigmented epithelium OR retinal pigment epithelium OR RPE: - 408621

Search Terms MCI

Mild cognitive impairment OR mild cognitive failure OR Mild cognitive dysfunction OR MCI OR amnestic MCI OR Amnestic mild cognitive impairment OR mild dementia: - 211354

OCT AND MCI: - 2254 documents (28 potentially relevant documents).

Search Terms Delirium

Delirium OR Acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain dysfunction OR acute brain failure OR metabolic encephalopathy OR acute psychoorganic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR Toxic psychosis OR Toxic confusion OR obnubilate OR or obnubilat*: - 636090

OCT AND Delirium: - 7405 documents (No relevant documents).

CINAHL

Search Terms OCT

Optical coherence tomography OR OCT OR SDOCT OR SD-OCT OR Retinal nerve fiber layer OR retinal nerve fibre layer OR nerve fiber layer OR nerve fibre layer OR Ganglion cell layer OR ganglion cell inner plexiform layer OR GCIPL OR retinal pigmented epithelium OR retinal pigment epithelium OR RPE: - 40254

Search Terms MCI

Mild cognitive impairment OR mild cognitive failure OR Mild cognitive dysfunction OR MCI OR amnestic MCI OR Amnestic mild cognitive impairment OR mild dementia: - 12806

OCT AND MCI: - 218 documents (13 potentially relevant documents).

Search Terms Delirium

Delirium OR Acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain dysfunction OR acute brain failure OR metabolic encephalopathy OR acute psychoorganic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR Toxic psychosis OR Toxic confusion OR obnubilate OR or obnubilat*: - 15960

OCT AND Delirium: - 677 documents (No relevant documents).

Cochrane

Search Terms OCT

Optical coherence tomography OR OCT OR SDOCT OR SD-OCT OR Retinal nerve fiber layer OR retinal nerve fibre layer OR RNFL OR nerve fiber layer OR nerve fibre layer OR Ganglion cell layer OR ganglion cell inner plexiform layer OR GCIPL OR GC-IPL OR retinal pigmented epithelium OR retinal pigment epithelium OR RPE: - 16304

Search Terms MCI

Mild cognitive impairment OR mild cognitive failure OR Mild cognitive dysfunction OR MCI OR amnestic MCI OR Amnestic mild cognitive impairment OR mild dementia: - 5903

OCT AND MCI: - 47 Documents (No relevant documents).

Search Terms Delirium

Delirium OR Acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain dysfunction OR acute brain failure OR metabolic encephalopathy OR acute psychoorganic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR Toxic psychosis OR Toxic confusion OR obnubilate OR or obnubilat*: - 5756

OCT AND Delirium: - 55 Documents (No relevant documents).

PsycINFO

Search terms OCT

Optical coherence tomography (kw) And “Ganglion cell (retina)” (MESH): - 2607

OCT (kw): - 2215

SDOCT (kw): - 5

SD-OCT (kw): - 42

SD OCT (kw): - 42

Retinal nerve fiber layer (kw): - 198

Retinal nerve fibre layer (kw): - 58

RNFL (kw): - 172

Nerve fiber layer (kw): - 228

Nerve fibre layer (kw): - 64

Ganglion cell layer (kw): - 281

Ganglion cell Inner plexiform layer (kw): - 14

GCIPL (kw): - 11

GC-IPL (kw): - 4

Retinal pigmented epithelium (kw): - 24

Retinal pigment epithelium (kw): - 177

RPE (kw): - 778

Summary of terms for OCT (using OR): - 5573

Search Terms MCI

Mild cognitive impairment (kw) and cognitive impairment (MESH): - 35464

Mild cognitive dysfunction (kw): - 52

Mild cognitive failure (kw): - 0

MCI (kw): - 6242

Amnestic MCI (kw): - 609

Amnestic mild cognitive impairment (kw): - 1287

Mild dementia (kw): - 835

Summary of terms for MCI (using OR): - 36511

OCT AND MCI: - 53 documents (10 potentially relevant documents).

Search terms Delirium

Delirium (kw) and (MESH): - 6515

Acute confusion (kw): - 126

Acute confusional state (kw): - 134

Acute organic psychosyndrome (kw): - 2

Acute brain syndrome (kw): - 35

Acute brain dysfunction (kw): - 14

Acute brain failure (kw): - 13

Metabolic encephalopathy (kw): - 68

Acute psychoorganic syndrome (kw): - 0

Clouded state (kw): - 2

Clouding of consciousness (kw): - 106

Exogenous psychosis (kw): - 19

Toxic Psychosis (kw) and toxic psychoses (MESH): - 262

Toxic confusion (kw): - 2

Obnubilate (kw): - 0

Obnubilat* (kw): - 18

Summary of terms for delirium (using OR): - 7125

OCT AND Delirium: - 3 documents (No relevant documents)

Web of Science

Search terms OCT

Optical coherence tomography OR OCT OR SDOCT OR Retinal nerve fiber layer OR retinal nerve fibre layer OR RNFL OR nerve fiber layer OR nerve fibre layer OR Ganglion cell layer OR ganglion cell inner plexiform layer OR GCIPL OR retinal pigmented epithelium OR retinal pigment epithelium OR RPE: - 1,369,965

Search Terms MCI

Mild cognitive impairment OR mild cognitive failure OR Mild cognitive dysfunction OR MCI OR amnestic MCI OR Amnestic mild cognitive impairment OR mild dementia: - 53,093

OCT AND MCI: - 364 documents (25 potentially relevant documents).

Search terms Delirium

Delirium OR Acute confusion OR acute confusional state OR acute organic psychosyndrome OR acute brain syndrome OR acute brain dysfunction OR acute brain failure OR metabolic encephalopathy OR acute psychoorganic syndrome OR clouded state OR clouding of consciousness OR exogenous psychosis OR Toxic psychosis OR Toxic confusion OR obnubilate OR or obnubilat*: - 85,471

OCT AND Delirium: - 1846 Documents (No relevant documents).

TRIP

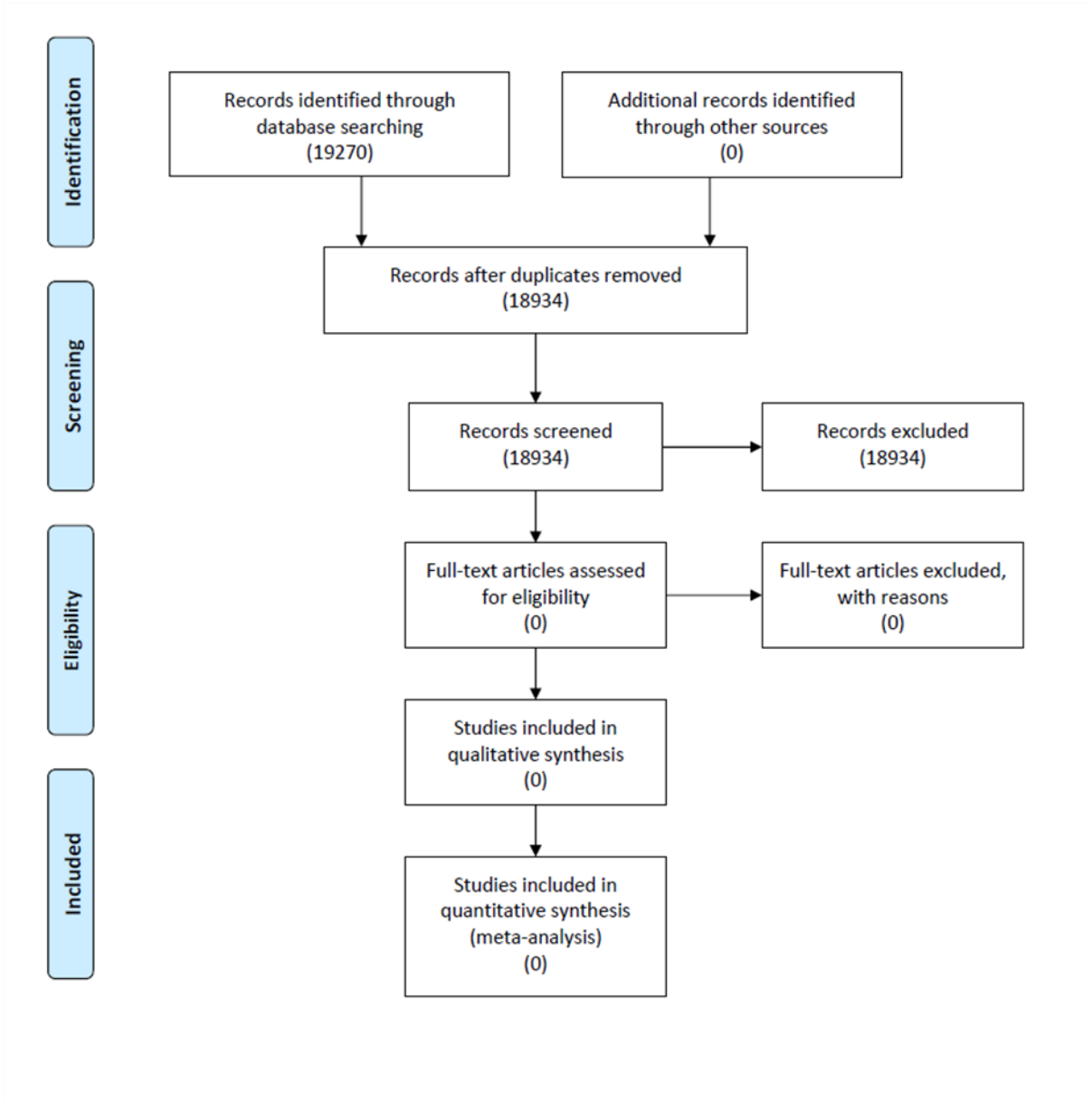
Search Terms OCT AND MCI

P (Mild cognitive impairment), I (Optical coherence tomography), C (Normal controls), O (left blank): - 67 documents (5 potentially relevant documents).

Search Terms OCT AND Delirium

P (delirium), I (optical coherence tomography), C (normal controls), O (left blank): - 7 Documents (No relevant documents).

Flow diagram for study processing- OCT and Delirium



Data items for OCT and MCI systematic review

Article information

Title, authors, year of publication, language, publishing journal, citation.

Study information

Prospective/retrospective data acquisition, source of cases, source of controls, number of cases, number of controls, sampling method, exclusion criteria, age of cases and controls, eye screening performed, brain imaging performed, blood tests, study groups, objective neurological assessment, objective cognitive test common to controls and MCI participants, blinding.

MCI

Criteria for diagnosis of MCI, type of MCI, duration between diagnosis of MCI and OCT.

OCT

OCT brand, OCT domain (time domain/spectral domain).

Eye used, OCT setting, centre of OCT image (e.g. optic disc or fovea).

Measurement software (platform or non-platform) or calipers, validation of segmentation, retinal layers measured and quality assessment of images.

Plots used (Early Treatment of Diabetic Retinopathy Study [ETDRS] quadrants or Hemispheric), reference to APOSTEL criteria (articles after 2016).

OCT measurement diameter, retinal measurements, p values, and authors' conclusions.

Modified QUADAS tool for systematic review of OCT in MCI/delirium

Population: People aged > 64 years

Recruitment pattern

Prior tests for retinal pathology

Index test: OCT

Target Condition: Delirium or Mild Cognitive Impairment

Reference Standard

Delirium: DSM IV

Mild cognitive impairment: Petersen Criteria, Winblad criteria, NIA-AA criteria, MoCA

Domains	Patient Selection	Index test	Target condition and Reference Standard	Flow and Timing
Risk of Bias	• Was a consecutive or random sample of patients enrolled? • Were controls age matched with cases? • Did the study avoid inappropriate exclusions? • Did the study screen out other known causes of retinal layer anomalies?	• Were the index test results interpreted without knowledge of the results of the reference standard? • Was there a process of quality control of the retinal images?	• Is the reference standard likely to correctly diagnose the target condition?	• Was there an appropriate interval between OCT and neurologic assessment? • Did all patients receive the same neurologic test? • Were all patients included in the analysis?
Applicability	Are there concerns that the included patients and setting do not match the review question?	Are there concerns that the OCT, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the question?	

Table X: Modified QUADAS – 2 tool