Chronic and Acute Systemic Inflammation and Long-Term Cognitive Decline

DISSERTATION

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Abstract

Chronic inflammation is commonly proposed to contribute to brain dysfunction in various medical conditions and aging processes. Additionally, acute inflammation has also been frequently proposed to threaten brain integrity in patients requiring critical care for infections, including, most recently, Sars-Cov-2 infection.

Both chronic and acute inflammation occur among cardiac surgery patients. These processes may, individually or combined, contribute to cognitive impairment. Examination of inflammatory levels both before and after surgical intervention among heart surgery patients requiring critical care enabled examining both inflammatory processes on long-term cognition in three separate study cohorts. Importantly, this kind of direct investigation of two important aspects of inflammation and cognition in the same cohort has not been done before. Cardiac surgery patients offer the chance to investigate the non-septic effects of chronic and acute inflammation on long-term cognition.

Study one examined a cohort of 125 *transcatheter aortic valve implantation* (TAVI) patients (mean age 80.5 years) monitored at the intensive care unit. All patients had comparatively low cognitive performance prior to surgery based on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Strong main effects of elevated pre-surgery levels of C-Reactive Protein (CRP) and Interleukin-6 (IL-6) and a higher propensity to develop post-operative *systemic inflammatory response syndrome* (SIRS) on cognitive performance over 12 months were revealed, i.e., associations with poorer cognition were shown to begin *prior* to surgery, and it continued throughout the follow-up period. The actual cognitive *trajectory* over time was modified by Interleukin-8 peak level after surgery, with a more significant decline in cognition. The opposite was true for presurgery Leukocyte counts, with a more rapid improvement in cognition over

time. The cognitive trajectory was not modified by the event of SIRS or by either chronic or acute levels of CRP, Procalcitonin, or IL-6.

Study two examined a younger sample of 215 cardiac surgery patients (mean age 69.7 years) over six months who underwent one of two types of heart valve implant (mitral or aortic) or a coronary artery bypass graft using a narrow panel of three inflammatory markers. This population was altogether cognitively healthier compared to that of study one. The primary measure used was the Mini-Mental Status Examination. The acute rise and absolute peak levels of the inflammatory marker CRP were negatively associated with a global cognitive screening score six months later, after controlling for presurgery cognition, although the effects were small. The clinical syndrome of SIRS did not associate with cognitive performance over time. A subset of patients in this study was given more in-depth cognitive examinations, which yielded similar results.

Study three used a broader panel of inflammatory biomarkers and an in-depth neuropsychological examination in a small sample of 31 major surgery patients aged an average of 64 years. Almost all underwent cardiac surgery and were kept in the intensive care unit for monitoring. SIRS diagnosis was negatively correlated with working memory (digit span backward) and positively with presurgery IL-6. S100 post-surgery at Visit 2 negatively correlated with delayed verbal recall (VLMT Trial 7). Different relationships for individual cytokines, notably procalcitonin, and Interleukin-6, explain variance in global cognition or verbal delayed recall. Hence, there appears to be an association, albeit different, depending on the particular inflammatory measure between acute systemic inflammation and long-term cognitive performance. Several pre-operative inflammatory levels did correlate with long-term cognitive performance.

Together these three studies show no simple, straightforward relationship between chronic or acute inflammatory states and cognition while controlling for age as an

essential biological factor. Hence, worse cognitive performance occurs in those experiencing higher degrees of inflammation, both chronic (i.e., sampled prior to operation) and acute (highest level after operation). What was not shown was a modification of the trajectory of cognitive performance itself, i.e., an overall strong association with inflammatory biomarkers on the general level of cognitive performance. Interaction effects between chronic and acute systemic inflammation were, on the whole, not supported by the data.

Glossary

AAR	Ascending Aortic Aneurism
Aß-42	A-Beta-42 is the amyloid protein associated with Alzheimer's Disease.
ACB or ACBG	Aortocoronary Bypass Graft (see also Coronary artery bypass graft surgery, CABG)
ACCP/SCCM	American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference
AD	Alzheimer's Disease
Adaptive Immunity	Adaptive immunity refers to immunological memory after an initial response to a specific pathogen.
AF	Atrial Fibrillation is a heart rhythm disorder characterized by rapid and irregular beating
Allele	One of a number of alternative forms of the same gene.
Amyloid	This is a class of extracellular protein deposits. Its lack of clearance (build-up) in the CNS is associated with various inflammatory and neurodegenerative diseases.
Aortic Aneurysm	This is the enlargement or widening of the aorta to the extent that it may rupture.
APOE	Apolipoprotein is responsible for breaking down proteins known as amyloid in the brain.
APOE4	Apolipoprotein E4, also APOE ҽ4 or APOE ε4, is an allele of a class of apolipoproteins associated with a higher risk of Alzheimer's Disease and cardiovascular diseases
ASD	Atrial Septal Defect refers to a congenital defect in the division of the heart's upper chambers.
AR	Aortic Regurgitation (also aortic insufficiency, AI) is the leaking of the heart's aortic valve, causing blood to flow backward.
AS	Aortic stenosis (AS or AoS) is the narrowing of the exit of the heart's left ventricle (where the aorta begins).
ASI	Acute Systemic Inflammation. Acute inflammation occurs when the body is subjected to injury, infection, or irritants.
ATS	American Thoracic Society
Autoimmunity	This refers to an organism's immune response against any of its own tissues, cells, or cell components.

AVR	Aortic valve replacement
Blood serum	Blood plasma without clotting factors; in other words, "pure" blood.
CABG	Coronary artery bypass graft surgery can create new routes around narrowed and blocked coronary arteries.
Cell-derived mediators	The primary cells involved in inflammatory responses include mast cells, neutrophils, eosinophils, macrophages, lymphocytes, endothelial cells, and platelets.
3Cell signaling	The ability of cells to perceive and correctly respond to their environment
CHF	Congestive heart failure is a chronic progressive condition in which fluid builds up around the heart, causing it to pump inefficiently.
CNS	Central Nervous System
Coronary Heart Disease	*coronary* (also called *ischemic) heart disease* is a partial blockage of coronary arteries causing insufficient blood circulation
CRP	C-reactive Protein is a protein produced by the liver and found in the blood after an injury, infection, or inflammation.
Chemokines	A family of small cytokines or signaling proteins secreted by cells.
Endothelium	This is the thin layer of simple cells lining the interior surface of blood vessels and lymphatic vessels.
Endotoxin	These are complex toxic molecules released by a number of Gram-negative bacteria. See LPS and PAMPs.
EF	Ejection Fraction is a measurement of heart failure that indicates the percentage of blood in the left ventricle pumped out at each contraction.
ICU	Intensive Care Unit
IL-6	Interleukin-6, also referred to as B-cell stimulatory factor-2 (BSF-2) and interferon beta-2, is a cytokine involved in various biological functions.
IL-8	Interleukin-8 is also known as neutrophil chemotactic factor CXCL8.
Immune System	Cells, tissues, and molecules that protect the body from numerous pathogenic microbes and toxins in our environment.
Immunity	Having sufficient biological defenses to avoid infection, disease, or another unwanted biological invasion.
Inflammation	Part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.
Inflammatory mediators	Soluble, diffusible molecules that act locally at the site of tissue damage and infection.

Innate Immunity	The immunity occurs naturally and does not arise from a previous infection or vaccination.
Ischemia	Ischemia is an insufficient supply of blood to an organ, usually due to a blocked artery
LPS	Lipopolysaccharides, also known as lipoglycans and endotoxin, are large molecules which elicit strong immune responses in animals. See also PAMPs.
LZ	Leukocytes are cells of the immune system that protect the body against infectious diseases and foreign invaders. LZ also refers to Leukocyte Count, the quantification of leukocytes (also White Blood Cell Count, WBC)
Lymph	Extracellular fluid is produced continuously by filtration from the blood.
Lymphocyte	A is any of three subtypes of white blood cells and is the primary type of cell found in lymph.
Monocytes	A type of white blood cell (leukocytes)
MCI	Mild Cognitive Impairment
MRSA	Methicillin-resistant Staphylococcus aureus. A type of staph bacteria resistant to many antibiotics.
multipotent	The adjective means having the potential of becoming any of several mature cell types
MVR	Mitral valve replacement
NSE	Neuron-specific enolase is an enzyme indicative of neuronal death found in neurons and cells of neuronal origin.
PAMPs	Pathogen-associated molecular patterns are numerous molecules recognized by cells of the innate immune system.
pathogen	Disease-producing agent, such as a virus, bacterium, or another microorganism
Phagocytosis	The process by which a cell engulfs a solid particle.
Phagocytes	Cells that protect the body by ingesting (phagocytosing) harmful foreign particles, bacteria, and dead or dying cells.
POCD	Postoperative Cognitive Dysfunction is a presumably transient impairment in cognition, mostly learning and memory.
PCT	Procalcitonin is a particular marker for clinically relevant bacterial infections and sepsis.
Proinflammatory cytokine	A type of cytokine that promotes systemic inflammation. Examples are IL-1 and TNF-α.

RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
Sepsis	Also known as blood poisoning, this is a body-wide inflammatory state in response to an infectious process.
SIRS	Systemic Inflammatory Response Syndrome is a clinical syndrome that is a form of dysregulated inflammation.
SIS	Surgical Infection Society
TNF-alpha	Tumor Necrosis Factor-alpha is a cell-signaling protein involved in systemic inflammation.
WBC	White Blood Cell Count (also Leukocyte Count, LZ)

Units of Measurement /Statistical terms

AUC	Area Under the Curve
cmH_2O	measurement of pressure
FiO_2	fractional inspired oxygen
g/l	gram(s) per liter
gL	gigaliter(s) (10^9/L)
H	hour
HR	hazard ratio
INR	International Normalized Ratio
IQR	interquartile range
µg	microgram(s)
MAP	mean arterial pressure
mg/dl	milligrams per deciliter
mg/l	Milligrams per liter
ml	milliliter(s)
mmHg	millimeters of Mercury (A measurement of pressure)
ml/kg h–1	milliliters per kilogram per hour
mmol/l	millimole per liter
O/E	Observed-to-Expected Ratio
PaCO2	alveolar carbon dioxide pressure
PaO_2	arterial partial oxygen tension
PaO2/FiO2	the ratio for the respiratory system
ROC	Receiver Operating Characteristic
RR	Relative Risk
SD	Standard Deviation
SE	Standard Error of Measurement

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Introduction

Older citizens often notice cognitive disorders after major surgeries and wonder if a major surgery may have contributed to their subjective experiences of cognitive decline. Neuropsychological examinations before or after non-head-related major surgery stays are still not common practice, although cognitive performance is sometimes used as a safety measure in studies of surgical procedures. At the same time, when a patient thinks they may have suffered cognitive impairment because of surgery, many potential other causes may be at play. Major surgery has been linked to post-operative cognitive decline (POCD) among older cohorts, which may last up to around three months post-surgery, but could last up to years (Steinmetz et al., 2013). Many studies of cardiac and non-cardiac surgery patients show cognitive impairment post-operatively up to years afterward (Abildstrom et al., 2000; Bartels et al., 2013).

Among the various underlying mechanisms of POCD, some may relate to the anesthesia used, and some are vascular, i.e., cerebral hypoperfusion, blood clotting, or embolisms. Safety studies of cardiac surgical methods have led to lowering such vascular risks and safer types and use of anesthesia. Another grouping of potential causes is a surgery-associated acute inflammatory response of the body, which may involve an autoimmune response within the brain. Speculation about inflammation as a mechanism for the cognitive decline has been frequent among those studying a wide variety of patients undergoing surgical procedures, intensive care stays, or significant infections such as pneumonia or, more recently, Sars-CoV-2 infection or those with diagnoses of neurodegenerative diseases. The connection between inflammatory responses of the body and brain health among major surgery patients requires careful and systematic examination. So far, this has not been undertaken, despite much speculation in scoping reviews and opinion editorials in the scholarly literature.

Elevated levels of *acute systemic inflammation*, common among heart surgery patients and intensive care patients, may have long-term consequences for brain health and cognition. Negative associations between acute systemic inflammation and cognition immediately post-surgery have also been reported (Rønning et al., 2010). However, the relationship between long-term post-operative cognitive impairment and acute systemic inflammation has only been speculated. Indeed, studies have tended to conflate the effects of chronic and systemic inflammation (Hudetz et al., 2011) even in the study of acute effects.

Studies of persisting postoperative cognitive decline do not agree on attributing causes. Some estimate as many as 42% having impairment up to 5 years post-surgery (Newman et al., 2007), and others attribute this to the underlying cardiac disease rather than surgery. The potential mechanisms of such impairment are also multitudinous, and there is a lack of systematic investigation which would enable the teasing out of the contribution of chronic versus acute inflammation on cognitive ability (Floyd & Giovannetti, 2012; Mayr et al., 2016; Rasmussen et al., 2001).

This investigation brings together strands of research from several fields. First is the study of chronic inflammation in neurodegenerative and cardiovascular disease and healthy epidemiologic studies. Second is the study of surgery patients and critically ill patients in the years after intensive care stay, which has centered on the experience of delirium. Third are studies of critically ill patients with sepsis and acute respiratory disease who, like a considerable portion of major non-cardiac surgery patients (as much as 45%), do not fully recover after surgery to previous cognitive ability (Cunningham, 2011; Gunther et al., 2012; Holmes et al., 2009a; McDonagh et al., 2010). While many studies point to the causative effect of the state of delirium in the perioperative period, delirium does not account for all patients who do not recover cognitively (Girard et al.,

2010). One underlying cause of delirium is, in fact, acute systemic inflammation (Cerejeira et al., 2010).

The effect of acute systemic inflammation is the subject of current investigation among sepsis patients, an acute systemic inflammatory disease state caused by a local source of infection (Semmler & Widmann et al., 2013). Whether the systemic inflammatory state causes cognitive impairment or whether another underlying process (infectious pathogen) is the leading cause is unclear (Widmann & Heneka, 2014). Unfortunately, the study of sepsis patients precludes the possibility of measuring cognitive ability prior to onset. The same type of massive inflammatory response regularly occurs after cardiac surgery or other major surgery due to tissue trauma during an operation.

Hence, teasing apart the associations of acute versus chronic inflammation in operative patients would provide much-needed clarity on two fronts:

1) To what extent can long-term cognitive impairments in this population be associated with chronic inflammation?

2) What is the specific effect of acute systemic inflammation in this population beyond chronic inflammation?

There is evidence from various animal models of acute systemic inflammation show cognitive impairment (especially learning and memory) as well as *central nervous system dysfunction* (especially in the hippocampus) after the resolution of the initial inflammatory response (Steckert et al., 2013; Tancredi et al., 2000; Weberpals et al., 2009).

This may be due to intimate structural connections between the limbic system and the hypothalamus, which has a crucial role in the immune-brain connection. Human correlational studies have shown that acute systemic inflammatory events are associated

with increased levels of *proinflammatory cytokines* (small proteins that are important in cell signaling during the inflammatory response) as well as increased rates of cognitive decline in various populations (Alley et al., 2008; Cunningham & Hennessy, 2015; Gorelick, 2010; Miller & Spencer, 2014; Paine et al., 2014). It has been hypothesized that stimuli such as tissue *trauma* due to surgery trigger a *peripheral systemic inflammatory response* precipitating a neuroinflammatory response leading to cerebral brain dysfunction and coincident cognitive impairment, expressed acutely as delirium, a temporary state of cognitive impairment (Lyman et al., 2014; Widmann & Heneka, 2014).

The postoperative inflammatory response is associated with short and medium-term and potentially also with long-term cognitive dysfunction, particularly in memory, after surgery in humans (Grape et al., 2012; Peng et al., 2013; van Harten et al., 2012) and animals (Cibelli et al., 2010). Specifically, a diagnosis of *"Post-operative cognitive dysfunction" (POCD)* has been identified as among the neurological deficits post-cardiac surgery together with systemic inflammatory response syndrome (Abildstrom et al., 2000; Eagle et al., 1999; Johnson et al., 2002), in an estimated 25-80% of patients (Funder et al., 2009).

Chronic systemic inflammation is suggested to be a driver of neurodegenerative processes in the central nervous system (Cunningham, 2013; Sankowski et al., 2015). In mild to severe community-dwelling Alzheimer's patients, Holmes et al. (2009) found that about 50% of 300 subjects had acute systemic inflammatory events in their medical history and that higher levels of the cytokine *tumor necrosis factor-alpha (TNF-α)* were associated with higher rates of cognitive decline throughout their 6-month follow-up. A study of inflammatory response in a small group of *mild cognitive impairment (MCI)* and *Alzheimer's Disease (AD)* patients indicates that specific cytokine signatures may predict

progression from MCI to AD (in particular, TNF-α, COX-2, IL-6, and INF-α; (Bermejo et al., 2008; Poole et al., 2016). Genetic variations such as AD-associated *Apoliprotein epsilon-4 (APOE4)* gene and specific alleles of single-nucleotide polymorphisms (SNPs) of numerous other genes that modulate the inflammatory response and may contribute to the pathophysiology of neurologic injury among cardiac surgery patients (Behnes et al., 2013; R. A. Benson et al., 2016; Drabe et al., 2001; Finch & Morgan, 2007; Mahley & Huang, 2012; Maury et al., 2021; Nakada et al., 2018; Ophir et al., 2005; Podgoreanu et al., 2006). It is beyond the scope of this work to cover all gene polymorphisms that may contribute to increased inflammatory response, but much research continues in this area.

Chronic inflammation may be linked to acute systemic events. Chronic inflammation measured by cytokines can precipitate acute inflammation with an acute increase in cytokine levels. Further, after recovery from an acute systemic inflammatory event, a return to baseline cytokine levels does not occur, but a new, higher level of circulating cytokines after systemic inflammation is maintained. A conceptual model has recently been proposed in which patients may never return to baseline levels but follow a new trajectory of higher inflammation/hemostasis levels in an age-dependent manner (Kale & Yende, 2011).

It is already known that age-related changes lead to higher levels of inflammation in the absence of acute inflammatory events and that these may directly have an impact on cognition, particularly memory (Simen et al., 2011). There is evidence of an association between inflammation and several age-related pathological conditions such as AD and Parkinson's disease (Hirsch & Hunot, 2009; Holmes et al., 2009b; Trollor et al., 2010). Furthermore, peripheral serum inflammatory cytokines are also associated with psychiatric conditions such as posttraumatic stress syndrome, depression, suicidal behavior, ideation, and perhaps schizophrenia (Brudey et al., 2015; Brundin et al., 2015;

Eraly SA et al., 2014; Eurelings et al., 2015; Michopoulos et al., 2015; Watkins & Andrews, 2015), which also are accompanied by cognitive changes, including memory.

Further, daily experiences such as stress, sleep disturbance, and sleep deprivation are also associated with higher levels of inflammation (Black, 2002; Grippo & Scotti, 2013; Irwin et al., 2015). The relationship between these conditions and systemic or neuroinflammation remains unclear since some inflammatory cytokines appear to be antecedent and some after the condition's onset, and most research to date has been correlational. This study represents a step toward disentangling the potential contribution of systemic inflammation to changes in cognition by investigating a group of acute systemic inflammation (in the absence of infection) in an age group already affected by the aging process, in which inflammatory cytokines are already higher.

Chronic and acute inflammation dynamics have been neglected as a mechanism for worse long-term cognitive performance. Hence, the differential associations of chronic versus acute systemic inflammation to cognitive ability warrant systematic and careful study in three cohorts of cardiac and general surgery patients.

Theoretical Background

This set of studies investigates the association of chronic and acute systemic inflammation on long-term cognition in three cohorts of operative patients, of which two are heart disease collectives, and one is a general collective of operative patients from a hospital intensive care unit, of whom the majority are also cardiac surgery patients. The studies' primary objective is to establish the association of chronic inflammation with long-term cognitive decline and systematically evaluate the add-on effect of *acute* systemic inflammation on cognitive ability post-surgery.

This is important since a differentiation between these two types of inflammatory states (chronic versus acute) has not yet been systematically studied, and, in addition,

there is much controversy about whether cardiac disease or cardiac surgery causes cognitive decline. Acute inflammation has been speculated to contribute to cognitive decline in other diseases and conditions, such as sepsis, burn, or trauma patients. However, studies of these cohorts preclude a measure of cognition prior to the acute systemic inflammatory events.

Recent work using endotoxins to induce an acute systemic inflammatory state in young adult healthy volunteers shows mixed evidence for a mildly negative effect on cognition (Bollen et al., 2017). However, acute systemic inflammation after cardiac surgery is much more significant and should theoretically have a much greater effect on cognition. While short-term effects are well established in the immediate perioperative period, it is unclear whether the level of this type of strong acute systemic inflammation has long-term adverse effects on cognition. This thesis operationalizes acute systemic inflammation by the "systemic inflammatory response syndrome" and biological measures of inflammation (cytokine levels, leukocyte) in the perioperative period. These will be analyzed in association with *long-term* cognitive performance (operationalized here as 6-12 months after surgery).

This work will draw specifically on the body of animal models showing detrimental effects of acute systemic inflammation on short and long-term cognition (S. Benson et al., 2017; Khan et al., 2019). This work will lead to a better understanding of the specific contribution of acute inflammation to long-term cognitive health in major surgery patients so that those experiencing such events can be better cared for: e.g., receive potential preventive treatment such as pre-rehabilitation, neuroprotective treatment via perioperative anti-inflammatory therapy, post-operative neuropsychological rehabilitation. In addition, this work will inform the research of similar acute

inflammatory conditions with and without infection, such as sepsis, trauma, burns, pancreatitis, ischemia, hemorrhage, and viral infections such as Sars-CoV-2.

The topics covered in the following sections are pertinent to the interpretation of this study. These include an overview of chronic cardiovascular disease and its mechanisms, cardiac disease and systemic inflammation, *Post-operative cognitive decline (POCD)* and its links to dementia and potential pathophysiology, cognitive impairment relating to inflammatory cytokines in healthy, aged, and cardiac disease or cardiac surgery populations including, the concept of "inflamm-aging" and a brief review of various sources of increased cytokine levels other than surgery or aging.

Cardiovascular Disease

Cardiovascular disease (CVD) refers to a collection of circulatory system diseases. This includes *coronary* (also called ischemic) *heart disease* (CHD, disease of blood vessels carrying blood to the heart), *cerebrovascular disease* (disease of blood vessels supplying blood to the brain), *peripheral vascular disease* (disease of blood vessels supplying the arms and legs), and *heart failure* (HF), among others. A combination of risk factors underlies cardiovascular disease, such as tobacco use, unhealthy diet, obesity, physical inactivity, harmful use of alcohol, hypertension, diabetes, and hyperlipidemia (World Health Organization, 2021). *Atherosclerosis*, a disease process underlying cardiovascular diseases, worsens over decades, although the disease process starts early in life. When severe, atherosclerosis can lead to the need for cardiac surgery to repair blood circulation through the heart.

Cardiac surgery patients experience years of chronic inflammation due to atherosclerosis, associated with poor cognitive functioning. During surgery, such patients are exposed to tissue trauma, triggering an acute systemic inflammatory response. Of note, an acute systemic inflammatory response is not separate from chronic inflammation

since many of the same biological processes are involved in chronic and acute inflammation. They are, for example, measurable using the same types of inflammatory cytokines in the blood.

Cardiovascular disease and the effects of aging on cognition may have common risks (such as smoking, inactivity, obesity, diabetes, high blood pressure, and high cholesterol) and common mechanisms, especially atherosclerosis and ischemia (Qiu & Fratiglioni, 2015). The broad concept of vascular cognitive impairment (VCI) refers to cognitive decline associated with CVD and includes, in its most extreme form, Vascular Dementia (VaD), the second most frequent type of dementia after Alzheimer's Disease (Goodman et al., 2017; Rizzi et al., 2014). Chronic systemic inflammation, associated with underlying atherosclerosis, is related to cognitive impairment and decline two decades later in elderly individuals with pre-existing CVD (Weinstein et al., 2017).

Post-Operative Cognitive Decline (POCD)

It is estimated that POCD decline occurs in 20-70% of patients after coronary artery bypass graft in the first week of surgery (Stroobant et al., 2008). The recovery period has often been assumed to be three months, at which point patients may return to baseline cognitive performance levels, yet this number is a subject of controversy. Whereas some reports indicate no more significant rates of cognitive decline after cardiac surgery, others report that even five years post-surgery, 30% of patients present cognitive impairments (Avidan & Evers, 2016; R. A. Benson et al., 2016; Berger et al., 2015).

The term POCD is loosely defined in several ways: minimal "changes in cognition," "a subtle impairment of memory, concentration, and information processing that is distinct from delirium and dementia" (Monk & Price, 2011), "resembles a mild cognitive disorder" that is "distinct from delirium and dementia," and may be associated with "functional limitations" during the early or late post-surgery period (Funder et al.,

2010; Maze & Todd, 2007). Depending on the study, cognitive decline post-surgery has been variously defined. In some studies, it is defined as the occurrence of one or more measures within a cognitive test battery of at least one standard deviation below a standard. This standard differs from one study to another. It is sometimes the baseline scores from within the sample, those of a healthy control group, or those of published historical norms. However, a much more stringent operationalization was used in the longitudinal International Study of post-operative Cognitive Dysfunction (ISPOCD) identified POCD in non-cardiac patients over 60 years of age up to three months post-operation (Abildstrom et al., 2000). This study defined POCD as a negative change in global cognition of a *z* score of at least -1.96 compared to baseline.

Hence, the large variance in incidence may be due to the different populations studied, the timing of assessments, and cognitive assessment instruments (Rasmussen et al., 2001). The incidence of POCD is low after minor surgery. Regional anesthesia does not seem to reduce the incidence of POCD. Whether an extracorporeal pump was used during cardiac surgery is an important factor in POCD is still unclear, and studies are contradictory (Kennedy et al., 2013; Kowalewski et al., 2016; Pérez-Belmonte et al., 2015).

Post-operative cognitive dysfunction has been found in patients with various types of major surgery, both noncardiac and cardiac surgery. Incidence of POCD was initially reported only after cardiac surgery, with the first reports appearing in the mid to late 1970s (Devereaux & Partnow, 1975; Willner et al., 1976; Willner & Rabiner, 1979). This finding holds most true in the immediate post-operative seven days for older patients over 60 years of age and has been studied most frequently in cardiac surgery patients, particularly those undergoing cardiopulmonary bypass graft surgery. Similar findings have been found in non-cardiac surgery patients and certain surgery patients up to 5 years

post-surgery (Fontes et al., 2013; Newman et al., 2007). The incidence varies significantly in the months after surgery (Funder et al., 2010; Steinmetz et al., 2009). Some examining the neuropsychological profile after coronary artery bypass surgery (both on- and off-pump) have shown only mild decline (less than half a standard deviation from baseline six years post-surgery) across all cognitive domains (Selnes et al., 2009). Patients with cardiovascular disease followed in this same study also showed long-term worsening of cognitive ability. Hence, atherosclerosis itself may have been the underlying cause rather than surgery.

The Prevalence of Post-Operative Cognitive Dysfunction (POCD)

The prevalence of post-operative cognitive dysfunction (POCD) after cardiac surgery is 25-80%, depending on the definitions and the type of surgery employed (2009). Incidence of POCD in cardiac surgery patients ranges from 30-65% post-surgery, within the next few months, 20-40% (Rasmussen, 2006). Rates of POCD in non-cardiac surgery populations are equally frequent (Paredes et al., 2016). Previous work on the pathophysiology of POCD leaves many questions open. It is unclear to what extent POCD lasts after surgery, like cognitive decline, and the exact causes due to multiple factors pre-, peri- and post-surgery, which is the subject of active research.

The causes of POCD among cardiac surgery patients may include cerebral hypoperfusion and oxygenation, cerebral microemboli, inflammation, type of anesthesia employed, systemic and cerebral inflammation, cerebral temperature changes, cerebral edema, and possible blood-brain barrier dysfunction (Bilotta et al., 2010; Fodale et al., 2010; Funder et al., 2009; Grocott et al., 2005; van Harten et al., 2012).

Neurological complications after cardiac surgery have been classified by the American College of Cardiology and the American Heart Association into two classes: Type-I are neurological complications such as stroke and transient ischemic attack, coma,

and fatal cerebral injury, and Type-II include delirium and post-operative cognitive dysfunction (POCD), including problems with memory, concentration, and psychomotor speed.

The pathogenesis of Type II is an area of active research, as it is multifactorial. One leading hypothesis is the involvement of neuroinflammation, which may derive from peripheral tissue damage due to changes in the blood-brain barrier (Hovens et al., 2016; Lyman et al., 2014). Greater sensitivity to general anesthesiology has been found due to inflammation, which may negatively affect brain integrity (Avramescu et al., 2016). Further, inflammation may cause various harmful effects on the brain, i.e., suppressing neurogenesis in the hippocampus or weakening microglial cells' normal ability to help repair and maintain synapses (Yirmiya & Goshen, 2011).

Aging is associated with increased inflammatory response and higher baseline levels of inflammation, as found in serum biomarker samples (Hein & O'Banion, 2012; Simen et al., 2011). Hence, there may be a bidirectional influence of aging and inflammation associated with cognitive change after acute systemic inflammatory events (Dilger & Johnson, 2008; Hudetz et al., 2011; Peng et al., 2013; Shah et al., 2013a). A POCD and inflammatory cytokines meta-analysis identified the main effects of S-100β, IL-6, NSE, IL-1β, and TNF-α, which studied some subset of these markers measured in the perioperative period (X. Liu et al., 2018). The number of patients in this analysis varied from 47 to 391, depending on the study. The origin of the cytokine concentration levels differed across studies (plasma versus serum). Most studies also reported large standard deviations. There is no information about the duration of POCD, nor how the definition of POCD may have varied across studies.

Conditions under which the immune system is strongly activated may be in the context of infection or injury and severe or chronic stressful conditions. In such cases,

glia and other brain immune cells change their morphology and functioning and secrete elevated levels of pro-inflammatory cytokines and prostaglandins. The production of these inflammatory mediators disrupts the delicate balance needed for the neurophysiological actions of immune processes and directly affects memory, neural plasticity, and neurogenesis.

Systematic Literature Review Inflammatory Biomarkers, Cognition in Cardiac Surgery Patients

The systematic review identified original articles measuring inflammatory marker concentrations and cognitive measures among subjects with cardiac surgery. The NIH National Library of Medicine PubMed search included the following terms:

("thoracic surgery"[MeSH Terms] OR ("thoracic"[All Fields] AND "surgery"[All Fields]) OR "thoracic surgery"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields]) OR "cardiac surgery"[All Fields] OR "cardiac surgical procedures"[MeSH Terms] OR ("cardiac"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "cardiac surgical procedures"[All Fields] OR ("cardiac"[All Fields] AND "surgery"[All Fields])) AND ("inflammation"[MeSH Terms] OR "inflammation"[All Fields]) AND ("cognition"[MeSH Terms] OR "cognition"[All Fields])

The two-level review is described in detail in

Table 1. The PubMed search on 12.08.2021 yielded eighty-three results. Further articles (N = 13) were found via reading the literature, perusing the reference lists, and included in the records.

Table 1

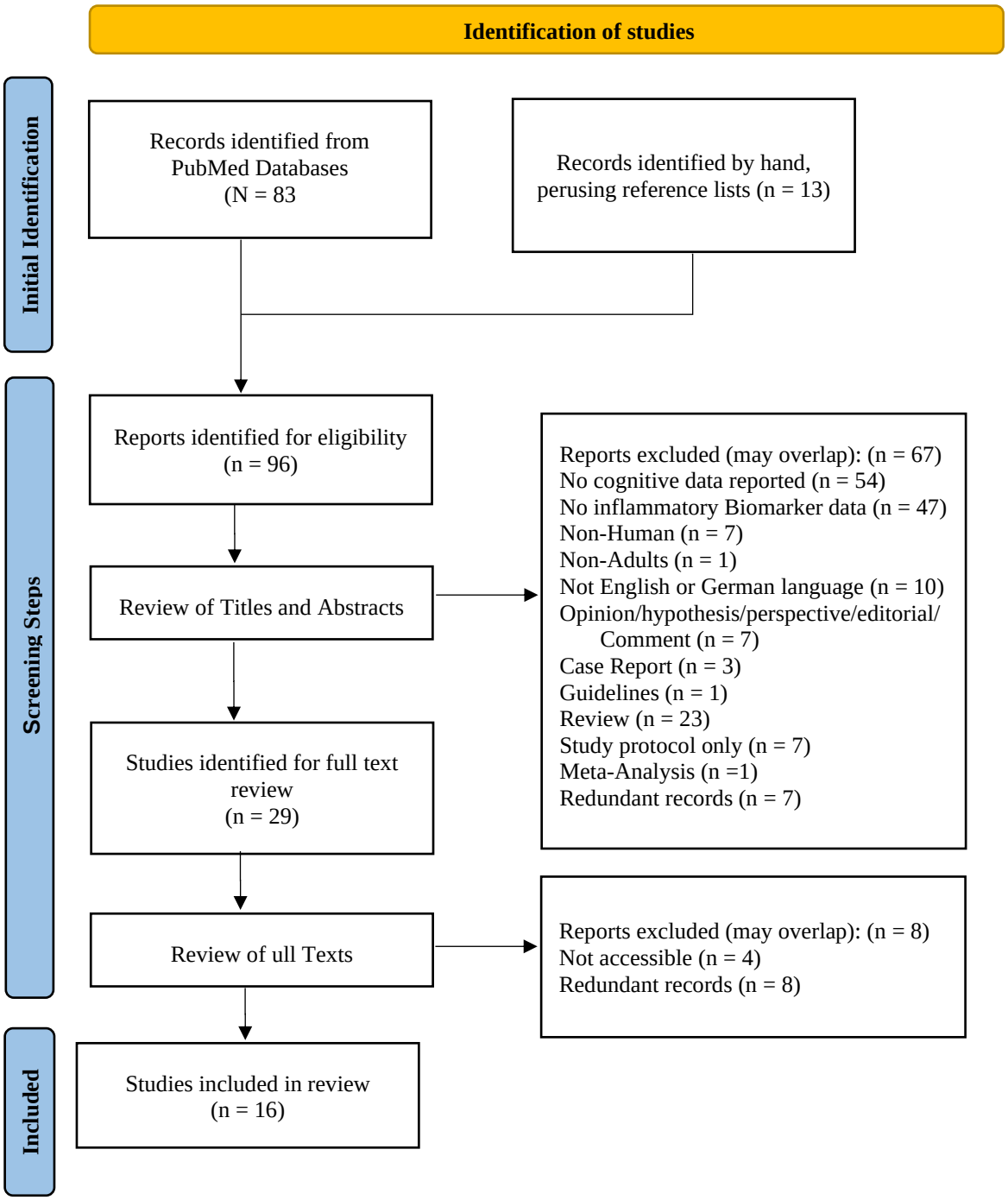
Screening questions for record exclusion at two levels of the review process

Level of review	Question	Answer
1 (Title and abstract)	Did an objective neurocognitive assessment (including short cognitive screenings) take place?	No
	Were objective inflammatory biomarker data reported?	No
	Were humans the subject of study?	No
	Were adults 18 and over the subject of study?	No
	Language of article English or German?	No
	Is the article an Opinion, hypothesis, perspective, editorial, or commentary?	Yes
	Was the record a case report?	Yes
	Was the record a guideline?	Yes
	Was the record a review?	Yes
	Was the record a meta-analysis?	Yes
	Was the record unique (not redundant)?	No
2 (Full article)	Should the article be excluded for any of the reasons listed above?	Yes

No automation tools were used for excluding entries. Each abstract and, if available, original manuscript were individually perused and selected by hand. The steps taken and

Figure 1

PRISMA 2020 Flow Diagram Systemic Literature Review



reasons for the inclusion and exclusion of each manuscript are depicted in Figure 1. The search was conducted to identify only studies of adult human beings who had undergone a cardiac surgical procedure and reported objective cognitive and inflammatory

biomarker data. The type of inflammatory biomarker, type of surgery, a control group, and exclusion criteria for cognitive or neurological status prior to surgery were reported but not used as filters. Based on the initial PubMed and manual search of reference lists, ninety-six records were initially identified. The essential information for each study (year of publication, author, Digital Object Identifier [DOI], PubMed Reference Identifier [PMID], title, and abstract) was entered into an excel spreadsheet. The exclusion criteria listed above were, likewise, entered into the spreadsheet. Based on the above exclusion criteria, the titles and abstracts of the 96 records were carefully screened (i.e., Review Level 1), yielding a total of 29 articles that reported cognitive outcomes (screening instruments and cognitive test batteries) and inflammatory measures (taken from serum, plasma, cerebrospinal fluid [CSF], gene analysis) among thoracic surgery patients of any type.

The reasons for the exclusion of sixty-seven records at Review Level 1 overlapped. Studies were excluded if they used any of the following: non-human subjects or non-adult subjects, reported no objective cognitive data, were written in a language other than English or German, reported no inflammatory Biomarker data, contained only opinions, only hypotheses, only perspectives, only editorials, only comments, only case reports, only guidelines, only literature reviews, only study protocols, or were meta-analyses.

In the next step (Review Level 2), the full texts were sought for the records. Each available full text was thoroughly perused. The essential information based on the full text for each study, including the type of neurocognitive test, population, and length of follow-up, was documented and put into an excel spreadsheet. Any further studies requiring exclusion at this stage were identified and excluded from further analysis.

The original manuscripts of the sixteen remaining studies were synthesized, and their relevant metrics collated in Excel. A summary of study design, cognitive measures,

biomarkers used, and the main findings of studies included in the review are included in Table 2-4. Most of the articles included in the final review came from the USA or Canada; five came from continental Europe (1 Belgium, 1 Denmark, 3 Germany), three from the United Kingdom, and one from Turkey. A broad time period of reported research ranged from 1999 to 2020. The sample of thoracic surgery patient populations examined was relatively homogeneous. Fourteen of the 16 studies examined patients undergoing Coronary Artery Bypass Graft (CABG), of which two studies had cohorts that also had undergone heart valve replacements (Guenther et al., 2013; Rudolph et al., 2008). One study only evaluated heart valve replacement patients (Uhle et al., 2018), and a single study examined noncardiac, non-neurosurgery thoracic surgery patients (Saxena et al., 2020).

The use and definition of cognitive decline among the reviewed studies varied. In five studies, no formal definition was reported (Geyik et al., 2015; Heyer et al., 2002; Sabe et al., 2015; Saxena et al., 2020; Skrabal et al., 2006). Four studies reported absolute value differences from pre- to post-surgery assessments. One study employed a reliable change index (RCI) score of -1.96 z-score (Forrest et al., 2011). Three studies used a cut-score below -1 SD baseline assessment (Mathew et al., 2007, 2009; Ramlawi et al., 2006). One study used a cut-score on cognitive screening (MoCA) in one study (Poole et al., 2016). Further delirium was employed as a definition of cognitive impairment in two studies: in one, a clinical delirium diagnosis at the bedside was used, and in another, a delirium scale was conducted (Guenther et al., 2013; Rudolph et al., 2008).

Although all sixteen studies in the final review met the formal criteria in the second round of assessing cognitive and inflammatory biomarker data in thorax surgery patients, fully 8 (50%) did not compare cognitive performance directly to the inflammatory biomarkers.

Within the eight studies that did make direct comparisons between inflammatory biomarkers and cognition, generally, three kinds of comparisons were reported: pre-operative cognition as a predictor of inflammatory response after surgery, inflammatory response after surgery predicting specific aspects of cognitive ability in the perioperative period, and third, inflammatory response after surgery as a predictor of 3-month post-operative cognitive ability. None examined a baseline inflammatory response or the rise in inflammatory response after surgery compared to long-term cognitive performance 6-12 months after surgery.

One study that diverged from the others in method examined the genetic predisposition regarding CRP response and cognition and found a greater risk of cognitive deficit six weeks after thoracic surgery due to a certain gene-variant (CRP 1059G/C SNP; Mathew et al., 2007).

Considerable variability in data and analyses makes it hard to assemble a cohesive picture. While one study indicated that pre-operative cognitive impairment could predict higher plasma IL-6 but not plasma CRP levels in the days just after surgery (Poole et al., 2016), another indicated that post-operative delirium was associated with higher acute-inflammatory levels in the days after surgery as calculated by an index value (25-plex; Rudolph et al., 2008). Another study evaluated four inflammatory biomarkers and cognition up to 3 months post-surgery, which reported an association between kynurenine and S100B, later memory performance, and between perioperative TNF-alpha and a Stroop task (Forrest et al., 2011). One study found no association between cognitive performance three months post-surgery and a panel of inflammatory biomarkers (Westaby et al., 2001).

Table 2

Systematic review country, sex, intervention, follow-up length results

Author, Year	Country	Sex (N / % female)	Age (yrs) (M, SD)	Intervention	Length of Follow-up
Christiansen et al., 2016	Denmark	6 / 14% f	Patients 63.5, 9.9 Healthy 23.0, 2.0	CABG, healthy controls	- 1d, 3d
Fitch et al., 2020	USA	data not shown	data not shown	CABG	1d, >1d [varied]
Forrest et al., 2011	UK	28 / 10.7% f	Patients 60.2, 1.7 Non cardiac 67.6, 1.4	CABG, non-cardiac thoracic surgery	6d, 3m
Geyik et al., 2020	Turkey	40 / 22.5% f	59.17, 9.11	CABG	0d, 7d
Guenther et al., 2013	Germany	221 / 35.3% f	Delirium 73.3, IQR 71.2–75.4 No Delirium 68.5, IQR 67.0-70.0	CABG, HVR, combined CABG–HVR.	7d
Heyer et al., 2017	USA	61/ 14.7% f	HCPB 64.7, 9.5 NHCPB 62.5, 11.3	CABG with either Heparin CPB or Nonheparin-CPB circuits during surgery	-3 to -7d, 5d, 6w
Mathew et al., 2007	USA	513 / 30.4% f	61.7, 10.5	CABG	6w
Mathew et al., 2009	USA	241 / 25.0% f	61.55, 12.9	CABG	6w, 1y
Poole et al., 2016	UK	193 / 9.3% f	67.46, 8.81	CABG	-30d
Ramlawi et al., 2006	USA	7 / 14.3% f	66.7, 10.5	CABG	4 to 5d

Table 2

Systematic review country, sex, intervention, follow-up length results (continued)

Author, Year	Country	Gender (N / % f emale)	Age (years) M, SD	Sample Characteristics	Length of Follow-up
Rudolph et al., 2008	USA, Canada	42/ 11.9% f	Delirium 74.7, 8.4 non Delirium 73.9, 7.0	CABG, HVR	6h, 4d
Sabe et al., 2014	USA	42/ sex not reported	data not shown	CABG	-10 to -1, 4d, 3m
Saxena et al., 2020	Belgium	38 / 42.1% f	64.8, 6.4	Noncardiac, non-neurosurgery operative patients undergoing surgical interventions of 1–4 h.	6h, 24h, 6w, 3
Skrabal et al., 2006	Germany,	39/ 17.9% f	63.5, 2.15	CABG	-2 to -1d, 7-10d
Uhle et al., 2017	Germany	38/ 34.2% f	SAVR 73, R 70-88 TA-TAVR 82, R 77-89 TF-TAVR 82, R 74-89	SAVR, TA-TAVR, TAVR	earliest time point after surgery [unclear]
Westaby et al., 2001	UK	100 / sex not reported	68, 8.0	CABG	3m

Note. f = female; IQR = Interquartile Range; CPB = Coronary Bypass; CABG = Coronary Bypass Graft; HRV = Heart Valve Replacement; SAVR= surgical aortic valve replacement; TA-TAVR = transcatheter aortic valve replacement; TAVR = transfemoral valve replacement; d = days; m = months; w = week; y = year.

Table 3

Systematic review of cognitive domains and inflammatory biomarker

Author, Year	Cognitive Domains Covered	Inflammatory Biomarkers
Christiansen et al., 2013	verbal and figural memory, language comprehension, attention, psychomotor processing speed, concentration, abstraction, visuospatial orientation	CRP, total white cell blood count, neutrocytes, lymphocytes, monocytes
Fitch et al., 2020	global cognition	LZ
Forrest et al., 2011	memory, attention, executive function	L-Tryptophan, L-kynurenine, kynurenic acid, 3HAA, AA, lipid peroxidation products malondialdehyde and 4-hydroxynonenal, neopterin, TNF- α, and S100B
Geyik et al., 2020	global cognition, verbal memory, attention, working memory	ICAM-1
Guenther et al., 2013	global cognition, delirium	LZ, CRP
Heyer et al., 2017	verbal memory, attention, psychomotor processing speed	TNF-α, IL-1β, and IL-6
Mathew et al., 2007	verbal and figural memory, language comprehension, attention, psychomotor processing speed, concentration, abstraction, visuospatial orientation	37 SNPs
Mathew et al., 2009	verbal and figural memory, language comprehension, attention, psychomotor processing speed, concentration, abstraction, visuospatial orientation	Caspase-3, CRP, IL-8, MMP-9, VEGF, and S-100β levels

Table continues

Table 3

Systematic review of cognitive domains and inflammatory biomarkers (continued)

Author, Year	Cognitive Domains covered	Inflammatory Biomarkers
Poole et al., 2016	global cognition	plasma IL-6, plasma hsCRP
Ramlawi et al., 2006	executive function, memory, learning, attention, working memory, naming, word fluency, premorbid intelligence	CRP, IL-1β, IL-10, LZ
Rudolph et al., 2008	global cognition	Cytokine 25-plex, death receptor 3-plex
Sabe et al., 2014	memory, executive function, attention, language, and global cognition	Microarray gene expression
Saxena et al., 2020	global cognition	IL-6 and HMGB1 levels
Skrabal et al., 2006	global cognition	plasma CRP, IL-6, PNE, C3a, b-TG
Uhle et al., 2018	global cognition	IL-2, -4, -6, -10, -17A, TNF-a, IFN-g; IL-1b, IL-18
Westaby et al., 2001	orientation, verbal memory, psychomotor speed, attention, speed of information processing	b-TG, IL-6, F1+2, D-D, C4a, TCC

Note. CRP = C-Reactive Protein; LZ = Leukocyte Count; SNP = single-nucleotide polymorphisms; IL = Interleukin; TNF- α = Tumor necrosis factor alpha; S100B = S100 calcium-binding protein B; 3HAA = 3-Hydroxyanthranilic acid; AA = anthranilic acid; ICAM-1= intercellular adhesion molecule-1; MMP-9 = matrix metalloproteinase-9; VEGF = vascular endothelial growth factor; 25-Plex = Panel of 25 different cytokines; b-TG = Beta Thromboglobulin; C3a = Complement Anaphylatoxin C3a; C4a = Complement C4 split product; D-D = D-

dimer; F1+2 = prothrombin fragment 1+2; hsCRP= high sensitivity C-Reactive Protein; IL = Interleukin; HMGB1 = High mobility group box 1 protein; LZ = Leukocyte Count; PNE = Polymorphonuclear Neutrophil Elastase; TCC = terminal complement complex; TNF-α = Tumor necrosis factor alpha.

Table 4

Systematic review definition of cognitive decline, statistical analysis, main findings

Author, Year	Definition Cognitive Decline	Statistical Analysis	Main Findings
Christiansen et al., 2016	absolute value pre- and post	Spearman correlations, Wilcoxon signed-rank test	No analysis of associations of inflammatory biomarkers and cognitive tasks.
Fitch et al., 1999	absolute value pre- and post	RM ANOVA, ANOVA, Chi-Square, Fisher's exact tests	No analysis of associations of inflammatory biomarkers and cognitive tasks.
Forrest et al., 2011	RCI, with a negative 1.96 z-score	ANOVA, T-tests, MWU, Pearson Correlation, Stepwise LR	Increased levels of kynurenine and S100B predicted lower memory performance. Increased levels of neopterin predicted lower color-word performance
Geyik et al., 2015	none	MWU, Wilcoxon, Chi-square, Spearman's rank correlation	No analysis of associations of inflammatory biomarkers and cognitive tasks.
Guenther et al., 2013	Occurrence of delirium as measured by CAM-ICU	MWU, Chi-Square test, MLR, stepwise backward-selection LR	No direct comparison between MMSE scores and cytokines was conducted.
Heyer et al., 2002	none	Student's t-test	No statement regarding the direct relationship between inflammatory biomarkers and cognition
Mathew et al., 2007	decline from baseline ≤ -1 SD for 1 or more of the 4 domain scores at 6 weeks after surgery.	FA, Pearson chi-squared and Wilcoxon rank sum tests, LR	Cognitive deficit was 16.7% in carriers of minor alleles at both loci compared with 42.9% in patients homozygous for the major allele. Absolute risk reduction in the observed incidence of POCD 20.6% for carriers of the CRP 1059C allele.

Table continues

Table 4

Systematic review definition of cognitive decline, statistical analysis, main findings (continued)

Author, Year	Definition Cognitive Decline	Statistical Analysis	Main Findings
Mathew et al., 2009	A decline of 1 SD or more in at least 1 of 4 domains	FA, Pearson Chi-Square, Fisher Exact, and t-tests. Linear Regression, LR.	No analysis of associations of inflammatory biomarkers and cognitive tasks.
Poole et al., 2016	A score below 26 points (of 31) on MoCA	t-tests, Pearson's correlations, independent t-tests, chi-square tests, hierarchical multiple linear regression	40% low cognitive functioning preoperatively. MoCA below 26 points predicted higher immediate plasma IL-6 level, but not hsCRP level.
Ramlawi et al., 2006	≤ -1 SD on 25% (2 of 8) administered tasks.	MWU, 2-way ANOVA, Spearman Correlation analysis	NCD 40.5% at baseline. Increase of CRP, IL-1ß, IL-10 of a significantly higher magnitude in those with NCD than in those without NCD
Rudolph et al., 2008	diagnosis of delirium	Student t-test	Chemokine index elevated in subjects who developed delirium in the early postoperative period.
Sabe et al., 2015	none	One-way ANOVA, Pathway Analysis	Patients with cognitive decline also had increased gene regulation associated with inflammation, cell death, and neurologic dysfunction.
Saxena et al., 2020	none	correlation paired Student t-test, linear mixed-effect models	Increase in peripheral IL-6 and HMGB1 and with cognitive impairment 6 weeks post-operatively. No analysis of associations of inflammatory biomarkers and cognitive tasks.

Table continues

Table 4

Systematic review definition of cognitive decline, statistical analysis, main findings (continued)

Author, Year	Definition Cognitive Decline	Statistical Analysis	Main Findings
Skrabal et al., 2006	none	Fisher's exact test, ANOVA, Tukey-Kramer Multiple Comparison Test, unpaired Student's t-test	No direct comparison between inflammatory biomarkers and cognition
Uhle et al., 2018	Change scores (pre-operative minus follow-up performance)	Friedman test, Kruskal–Wallis, Dunn's multiple comparisons, Wilcoxon rank test	No direct comparison between inflammatory biomarkers and cognition
Westaby et al., 2001	Change scores (pre-operative minus follow-up performance)	Correlation Analysis	Deterioration of the group mean in 5 of 11 neuropsychological measures three months post-surgery was found—no significant correlation between neuropsychological performance and maximum values of inflammatory biomarkers.

Note. ANOVA = Analysis of Variance; CAM = Confusion Assessment Method; FA = Factor Analysis; ICU = Intensive Care Unit; LR = Logistic Regression; MANOVA = Multivariate Analysis of Variance; MWU = Mann-Whitney-U; MLR = multivariate logistic regression; POCD = Postoperative Cognitive Decline; RMANOVA = Repeated Measures MANOVA; RCI = Reliable Change Index; HMGB1 = High mobility group box 1 protein; hsCRP = high sensitivity C-Reactive Protein; IL = Interleukin; LR = Logistic Regression; MoCA = Montreal Cognitive Assessment; MWU = Mann-Whitney-U; NCD = Neurocognitive decline; RCI = Reliable Change Index; SD = Standard Deviation.

Cognitive Impairment and Chronic Cardiovascular Disease

It has repeatedly been shown that *cardiovascular disease (CVD)* carries a risk of cognitive impairment and even dementia in the long term (Leritz et al., 2011; Vogels et al., 2007). This has been shown especially for CVD risk factors high blood pressure, diabetes, high cholesterol, obesity, and smoking. The higher risk of dementia is associated with various types of cardiovascular disease and cardiovascular risk factors in middle-aged to older adult populations (Harrison et al., 2014; Qiu & Fratiglioni, 2015). For example, *atrial fibrillation* (AF) is associated with a relative risk of 2.7 (95% *CI* 1.8–4.0) compared to that of the general population of 1.4 (95% *CI* 1.2–1.6; Kalantarian et al., 2013). Further, mild cognitive impairment was 24%, and impairment consistent with dementia was 15% in those with *heart failure (HF)* in the US Health and Retirement Study (Gure et al., 2012).

Little is written about the association between chronic inflammation associated with chronic heart disease and cognitive impairment or dementia incidence, but it has been speculated over the last 8-10 years. Chronic inflammation is one potential mechanism of many, which may interact in complex ways to lead to cognitive impairment or dementia. Age is associated with higher cytokine levels. Obesity is likewise associated with increased inflammatory cytokines (Gabuzda & Yankner, 2013; Miller & Spencer, 2014). Many disease states, including cancer, neurodegeneration, stroke, and trauma, also cause increased inflammation. There are many inflammation triggers, including negative experiences (Eurelings et al., 2015; Messay et al., 2012; Pellissier et al., 2014) and negative emotions (Black, 2002; Cohen et al., 2015; Irwin et al., 2015). There is also increasing evidence that inflammation may contribute to negative affect, including depression (Black, 2002; Grippo & Scotti, 2013; Irwin et al., 2015) and personality traits

(Mõttus et al., 2013). It is beyond the scope of this thesis to provide a comprehensive review of this important literature

Plaque Formation and Coronary Heart Disease

The etiology of coronary heart disease (CHD) is the buildup of a waxy substance, called plaque, inside the coronary arteries, which supply the heart with oxygen-rich blood. Plaques are fatty deposits of calcium, fat, cholesterol, cellular waste, fibrin (involved in blood clotting), and white blood cells, also known as macrophages, on the lining of the arteries in a complex manner (Moore & Tabas, 2011). Among the conditions and syndromes involved in CHD are a*therosclerosis*, a chronic inflammatory response of the walls of blood vessels, a thickening of the aortic valve known as *aortic sclerosis*, the narrowing of the exit of the left ventricle of the heart (where the aorta begins) termed *aortic stenosis (AS or AoS)*. Once aortic stenosis has become severe, treatment is usually valve replacement surgery. *Mitral Stenosis*, a narrowing of the mitral valve, is usually treated with a heart valve replacement.

Immune System

The immune system is a collection of cells, tissue, and molecules that protect the body from many pathogenic microbes and environmental toxins (Janeway Jr et al., 2005). The first line of defense is physical barriers, such as skin. The second line of defense is the innate immune system which consists of numerous mechanisms independent of previous exposure to pathogens and includes cells and proteins that are always present and ready to rapidly mobilize (within hours) and fight microbes at the site of infection. The third line of defense in humans and other vertebrates is the adaptive (also acquired) immune system, which is called into action against pathogens that can evade or overcome innate immune defenses, taking longer to respond than the innate immune system (days),

but acting much more powerfully. It should be noted that cells rely on the innate immune as a prerequisite for functioning the adaptive immune system and that the latter participates in the function of the former (Janeway Jr et al., 2005). The principal elements of the immune system relevant to this work will be presented briefly here, yet the immune system involves a vast array of cells and structures throughout the body, which interact in extraordinarily complex ways, any description of which would go far beyond the scope of this work.

Inflammation

Inflammation (Latin: “inflammare,” English: „to set fire") refers to a complex biological reaction of the innate immune system to protect the body from damaging stimuli, such as pathogenic (disease-causing) agents, damaged cells (trauma), or hemorrhage. Inflammation is a protective response, including immune cells, blood vessels, and molecular mechanisms. The goal of the inflammation is to eradicate the cause of cell damage to clear necrotic cells and tissue from the original insult and damage due to the inflammatory process and initiate tissue repair. Symptoms include pain, heat, swelling, redness, and loss of function. Although many infectious agents cause inflammation, many other biological stimuli, such as atherosclerosis and ischemia, cause inflammation. Inflammation refers solely to the body’s immuno-vascular reaction to a damaging stimulus, not the stimulus itself. Among the many underlying causes of inflammation are pathogenic agents (e.g., virus, bacteria), trauma, strenuous physical activity, stress, allergies, and high glycemic nutrition.

Acute Inflammation

Acute inflammation usually has a sudden onset and is temporally finite since it resolves (as opposed to *chronic inflammation*). It is depicted below in a simplified

example of acute local inflammation. Here, the cause of inflammation is a splinter in the skin, which enables pathogenic agents (e.g., bacteria) to enter the skin. This is detected by immune cells (mast cells), which send a chemical signal to recruit leukocytes (white blood cells) from the blood vessel to the source of injury in the skin using a series of biochemical signals. An important class of proteins involved in the cell signaling of this process is *cytokines,* described below, which represent markers of inflammation.

The blood cell wall (endothelium), normally tightly closed, spreads out (vasodilation) and allows leukocytes to pass between individual cells into the skin. After crossing the endothelium, leukocytes in the bloodstream (also called *monocytes)* are transformed into *macrophages*, which eat the invading pathogens and help clear dead tissue. Relevant to this study is that acute inflammation is the body's natural reaction to major surgery, even in the absence of infection.

Chronic Inflammation

Immune system changes are years in the making before *chronic inflammation* is established (Straub, 2017). If inflammation is prolonged (days, weeks, or years), macrophages assume permanent residence in the injured tissue. Levels of inflammatory cytokines and leukocytes circulating in the bloodstream are raised. There is a simultaneous process of healing *and* destruction in the inflamed tissue due to toxins (e.g., *reactive oxygen species*) released as part of the body's inflammatory reaction (Hong & Banks, 2014). Hence, tissue damage is also always implicated. Chronic inflammation is commonly induced by many diseases and conditions, including atherosclerosis, obesity, diabetes, rheumatic disease, and neurodegenerative diseases. Of importance to this study is the fact that cardiac surgery patients all have experienced years-long chronic inflammation.

Systemic Inflammation

Systemic inflammation occurs when the cause of inflammation spreads throughout the body via the circulatory system, including the bloodstream and lymphatic system. This is usually caused when inflammation increases and is not regulated. Systemic inflammation can be acute or become chronic, as in the case of cardiac disease patients. Acute systemic inflammation is thought to be symptomatologically manifested with these symptoms, and those diagnosed with SIRS also have elevated circulating cytokine levels. Nevertheless, having high levels of circulating cytokines does not directly translate into a diagnosis of SIRS (Ramlawi et al., 2006). The criteria for a diagnosis of SIRS are listed in Textbox ***1***.

Textbox 1. Systemic Inflammatory Response Syndrome (SIRS)

Systemic Inflammatory Response Syndrome (SIRS)

Systemic inflammatory response syndrome is a reaction of the body to infectious (virus, fungi, bacteria, parasite) or non-infectious injury (e.g., trauma, burns, ischemia, hemorrhage, major surgery). It may be clinically diagnosed if at least two of the following four criteria defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM) are fulfilled (Engel et al., 2007):

(a) temperature ≤ 36 or ≥ 38 °C;

(b) tachycardia with heart rate ≥ 90 beats per minute;

(c) tachypnea with ≥ 20 breaths per minute and/or paCO2 ≤ 32 mmHg or mechanical ventilation;

(d) white blood cell count ≤ 4 or ≥ 12 g/l and/or left shift ≥ 10%.

Cytokines

Cytokines (cyto, from Greek *"κύτταρο"* kyttaro "cell" + kines, from Greek *"κίνηση"* kinisi "movement") are a broad grouping of proteins that are produced by immune cells

(e.g., leukocytes). They help to initiate and regulate inflammation in the face of harmful stimuli. They are involved in several kinds of signaling acting via receptors in cell membranes to modulate the body's immune response.

Cytokines are divided into several classes, such as *chemokines* (which call in other cells to the site of infection), *interferons* (which inhibit viruses from replicating themselves*), interleukin*s (which regulate immune and inflammatory responses), *lymphokines* (attract macrophages to the site of foreign material), and *tumor necrosis factors* (destroy cells involved in the immune response). Depending on the type, cytokines can be *proinflammatory* (e.g., Interleukin-6 [IL-6], Interleukin-1 beta [IL-1β], Tumor necrosis factor-alpha [TNF-α]) or *anti-inflammatory* (e.g., Interleukin-4, Interleukin-10, Interleukin-13).

Cytokines Crossing the Blood-Brain-Barrier

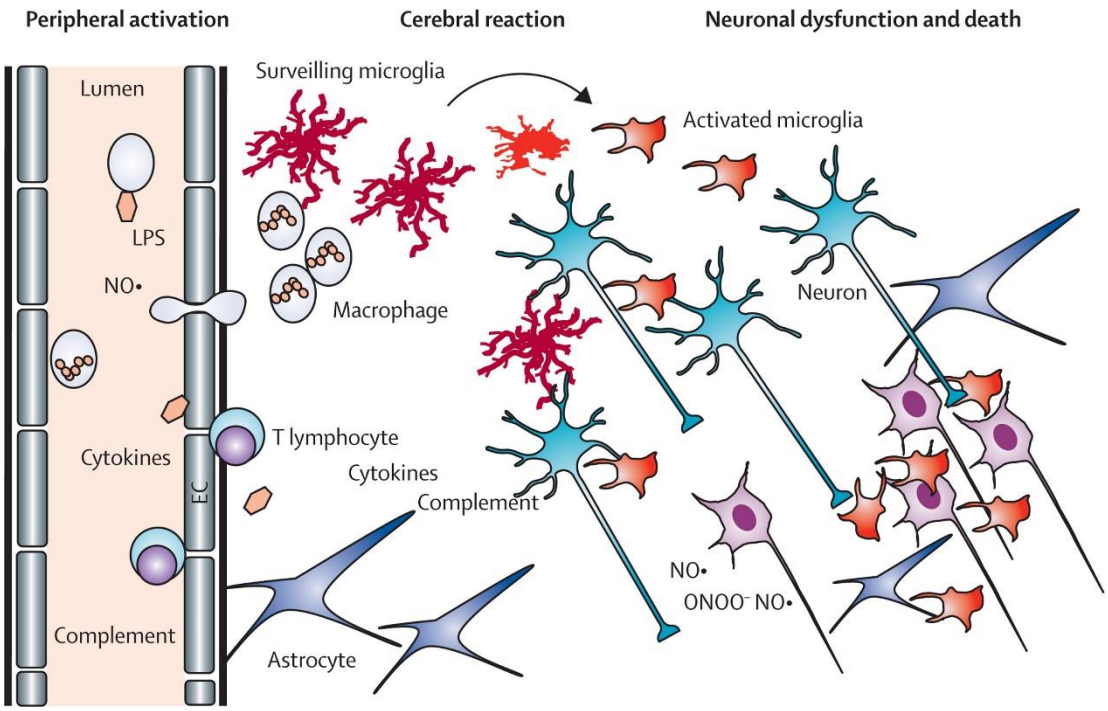
Systemic elevation of particular cytokines (e.g., TNF-alpha, IL-1beta, and IL-6) in mouse models has shown activation of inflammatory mediators in the brain, especially in the hypothalamus (Wei et al., 2015). It is hypothesized that peripheral cytokines penetrate the blood-brain barrier directly or indirectly via the vagus nerve, which stimulates a massive systemic inflammatory response (Xiong et al., 2009). Some studies indicate that peripheral inflammatory cytokines can cross the blood-brain barrier after surgery and may modulate CNS inflammatory processes resulting in neurodegeneration and impairing cognitive function (Lee et al., 2009; Marsland et al., 2015; Zuliani et al., 2007). Support for this comes from animal models, which show BBB disruption after-peripheral surgery and higher levels of peripheral cytokines associated with migrating macrophages into the hippocampus (Sudheimer et al., 2014). Behavior models also show changes in behavior after peripheral surgery in these mice.

Several innate immune components, including complement factors and pro-inflammatory cytokines, may reach deeper brain regions and even actively cross the BBB via specific pathways. One theoretical model of how peripheral immune activation may affect changes in the central nervous system and cause neuronal damage is depicted in Figure 2 (Widmann & Heneka, 2014).

Figure 2 represents a cerebral blood vessel and surrounding brain tissue after injection of *lipopolysaccharide* (LPS), a bacterium commonly used in animal models of systemic inflammation. LPS causes increased production of cytokines (e.g., IL-6, TNF-alpha) and other inflammatory mediators in the peripheral circulatory system. Inflammatory mediators and leukocytes damage the endothelial cells tightly packed along the BBB. This and vasodilation during inflammation cause increased BBB permeability.

Figure 2

Permeability of the Blood-Brain Barrier in an Animal Model of Systemic Inflammation.



Note. Widmann & Heneka (2014). Copyright 2014 Elsevier Ltd, all rights reserved.

Immune cells (including leukocytes and others), cytokines, and pathogens can cross the BBB theoretically, entering the brain itself (Widmann & Heneka, 2014). A massive inflammatory cerebral reaction to the entry of these proteins and cells may cause neuronal dysfunction or death. This is supported by hippocampal and cortical damage associated with inflammation-induced impairment of long-term potentiation and reduced learning and memory capacity in various animal models (Cassol-Jr et al., 2011; Comim et al., 2011; R. H. Field et al., 2012; Imamura et al., 2011).

Another possibility is the activity of an enzyme in the brain called *isoform of nitric oxide (NO)-producing enzymes (iNOS)* is expressed in macrophages, glial cells, and tumor cells in response to pro-inflammatory cytokines or endotoxin (Pomykala et al., 2013). iNOS activity may continue for days and result in cell death and tissue damage in the brain (Kim et al., 2001; Xie & Nathan, 1994).

Immune-activated NO generation exerts harmful effects on the brain via several mechanisms, and neurons are susceptible to sustained NO exposure (Heneka et al., 1998; Leist et al., 1997). Among the mechanisms concerned are protein nitrosylation and impairment of long-term potentiation impairments, and the inhibition of mitochondrial respiration, all of which cause pathological processing in the nerve cell and increase apoptosis (Brown, 2007; Calabrese et al., 2007; Moncada & Bolaños, 2006). Importantly, persistent NO-mediated changes have been found at the synapse level and are associated with impaired learning and memory (Fukunaga & Miyamoto, 2000; Stagi et al., 2005).

Several mechanisms may lead to neurodegeneration during systemic inflammation: crossing of peripheral immune cells and inflammatory molecules, such as TNF-alpha or IL-6 across the BBB, damage to oligodendroglial myelin sheaths, which lead to axonal degeneration, increase in the number of astrocytes which leads to more permeability of

the BBB and reduction of synaptic maintenance ((Sankowski et al., 2015). Lastly, microglial cells may also accumulate as a reaction to injury, ultimately leading to tissue deterioration.

Interaction Brain Immune System

Communication pathways between the CNS and the immune system involve immune mediators and cytokines that can cross the blood-brain barrier and signals sent via the vagus nerve or second messengers (Eskandari et al., 2003). The CNS can also signal the immune system via hormonal pathways, the *hypothalamic-pituitary-adrenal* (HPA) axis, and the hormones of the neuroendocrine stress response.

The mechanisms by which peripheral cytokines can affect brain function have been the subject of much debate. The precise mechanisms by which cytokines signal the central nervous system (CNS) are unknown, but possibilities include:

1) The direct entry of cytokine into the brain across the blood-brain barrier by a saturable transport mechanism,
2) The interaction of cytokine with circumventricular organs such as the organum vasculosum of the lamina terminalis [OVLT] and area postrema, which lack the blood-brain barrier, and
3) The activation of afferent neurons of the vagus nerve.

Peripheral inflammatory cytokines also appear to upregulate brain activity via the hormonal system. It is beyond the scope of this thesis to explain these processes at the molecular level. In summary, it has been proposed that peripheral immune activation appears to cause oxidative stress in the *subfornical organ (SFO)*, which amplifies the immune response in the periphery (Hindmarch & Ferguson, 2016) *and* affects the CNS *without any BBB permeability*. In addition, anatomically close and similar is the *organum*

vasculosum (OV), which also serves as a portal between peripheral inflammatory processes and the CNS without BBB permeability (Lechan, 2019).

These parallel feedback loops may appear in various cardiovascular conditions, such as hypertension and heart failure, but potentially also in other conditions such as multiple sclerosis, schizophrenia, depression, chemotherapy response in breast cancer, and diabetes Type 2 (Wei et al., 2013). Aging itself has long been thought to involve oxidative damage due to the interplay between oxidative stress (e.g., radical-free theory of aging, mitochondrial theory of aging) and antioxidant response, yet the mechanisms involved are complex and have not yet achieved consensus (Gemma et al., 2007; Sanz & Stefanatos, 2008).

Inflammatory Cytokines and Cognitive Ability

In human studies, higher levels of CRP and IL-6 in middle-aged adults (35-50 years) have been associated with worse, poorer spatial reasoning, short-term memory, verbal ability, learning, memory, and executive function, and brain morphological changes in gray and white matter volumes, hippocampus and cortical surface area (Marsland et al., 2015). Recent findings from a community-dwelling sample of those over 60 years of age in the Berlin Aging Study showed that elevated IL-6, IL-10, and CRP levels were negatively associated with executive function and processing speed but not with verbal episodic memory (Tegeler et al., 2016). The cognitive ability of this cohort remained in the normal range.

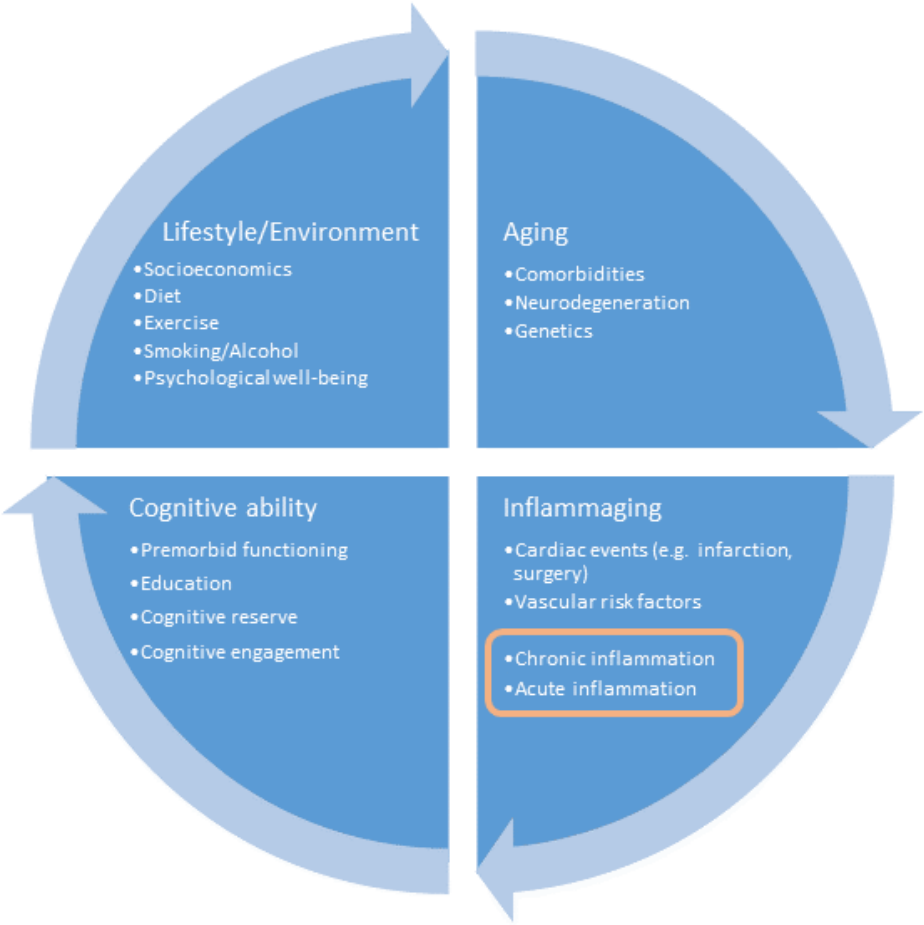
Inflammaging

Another concept central to populations requiring cardiac surgery is that of *"Inflammaging,"* the body's response to the accumulation of exposure to infections (mild and severe) as well as to substances that stimulate antibodies (called *antigens*) as one ages

(Figure 3). It has two main components: 1) raised levels of inflammatory cytokines circulating through the body and 2) changes to the immune system known as *"immunosenescence"* (Michaud et al., 2013). In other words, a potentially toxic imbalance in the individual's ability to withstand environmental factors causing inflammation both within and outside the body evolves.

Figure 3.

Multiple Factors Influencing Cognitive Outcomes Post Cardiac Surgery



Note. Adapted from Baylis et al., 2013; Qiu & Fratiglioni, 2015; Ramlawi et al., 2006.

Nevertheless, *immunosuppression*, i.e., worsening or weakening of immune response, represents a conundrum in immune response research in aged people. Factors

that may modify immune response include genotype, as both inflammaging and immunosuppression have a genetic component and imbalances in certain transmitter levels, such as cortisol (Baylis et al., 2013).

tthe myriad factors influencing cognitive performance in cardiac surgery are depicted in Figure 3. The cyclical nature of these relationships does not only go in a clockwise direction, and many interconnections are not depicted here for parsimony. It follows that lifestyle and environmental factors, aging processes, and inflammaging influence cognitive performance. *Pre-operative cognitive ability* (mental engagement, intelligence, education, cognitive reserve) conditions post-operative cognitive ability and *psychiatric burden* (stress, depression, anxiety, post-traumatic stress disorder) may also contribute to chronic inflammation and a worsening of cognitive performance. Acute inflammation may interact with chronic inflammation and hypothetically could independently contribute to the deterioration of cognitive performance. This schema only serves to give context to chronic and acute inflammation phenomena, which are the focus of the studies presented here. This treatise focuses on the nexus between chronic inflammation, induced acute inflammation, and cognitive performance in a series of well-characterized cardiac surgery patients for whom a preoperative cognitive status was assessed and post-operative performance in the medium to long-term.

Common Hypotheses

The main questions framing this thesis are to what extent chronic inflammation associates negatively with cognitive performance in the long term, and to what extent does a secondary, acute systemic inflammatory “hit” contribute to cognitive performance (i.e., serving as a model myriad inflammatory events). Thus, four main hypotheses will be examined across three studies:

Hypothesis 1: Are higher chronic inflammation levels associated with acute inflammation indicators?

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance at any time point?

Hypothesis 3: Do chronic and acute systemic inflammation influence the *trajectory* of cognitive performance over time?

Hypothesis 4: Is there an *interaction* between chronic and acute inflammation on cognitive performance?

Methods

Overview of Study Designs

An overview of the most relevant points of the three study designs is presented in Table 5, including population, age, sample size, and parameters and timing of assessments. Each one is of an observational analytic cohort nature. Each study examined the clinical diagnosis of systemic inflammatory response syndrome (SIRS) and pro-inflammatory cytokines for their potential negative associations with pre-operative and long-term cognitive performance. A brief outline of the objectives of each study will be presented next.

Study 1: Transcatheter aortic valve implantation patients. This study included 125 *Transcatheter Aortic Valve Implantation (TAVI)* patients who received the identical procedure with minimally invasive closed-chest surgery and were evaluated for long-term cognitive change at three days, three months and 12 months post-surgery. Cognition was evaluated with the help of a 30-minute standardized test battery, and inflammation was operationalized according to the clinical diagnosis of SIRS, as well as with blood chemistry panels which included serum C-Reactive protein (CRP), Procalcitonin (PCT),

Interleukin-6 (IL-6), Interleukin-8 (IL-8) and Leukocytes (LZ), which were measured prior to operation, as well as at several time points during the first week after surgery. Baseline cytokines and cognition were compared to a peak value of cytokines during the post-surgery period. There were no exclusion criteria regarding neurological or cognitive status.

Study 2: General cardiac surgery patients. A heterogeneous sample of 168 cardiac surgery patients with either a valve implant (mitral or aortic), a coronary artery bypass graft, or both was evaluated. Some surgeries were closed, others open-chested. Cognition was evaluated before surgery using the Mini-Mental Status Examination and a telephone variant of the MMSE six months post-surgery. Inflammation was operationalized as a diagnosis of SIRS or Sepsis (not further differentiated, as these are very similar diagnoses) and pre-operative blood panels, including CRP and Leukocytes. There were no exclusion criteria regarding neurological or cognitive status. A depression scale was also employed.

Study 3: General operative patients (majority cardiac surgery). Thirty-one major surgery patients, most of whom had cardiac or other major surgery, were evaluated pre-operatively using the MMSE; those obtaining less than 25 points were excluded. Also, anyone with central nervous system disturbance or disorder was excluded. Blood chemistry was assessed prior to surgery and at least one time-point after surgery at the intensive care unit (ICU). Inflammation was operationalized as a diagnosis of SIRS or Sepsis (a differentiation was made between these diagnoses) as well as a large panel of inflammatory cytokines, including CRP, PCT, IL-6, Neuronal Specific Enolase (NSE), S-100 calcium-binding protein B (S-100B), and Tumor Necrosis Factor-alpha (TNF-α). Cognition in the follow-up assessments was measured using an hour-long comprehensive

test battery, and psychiatric burden (depression, anxiety, posttraumatic stress, and somatic symptoms) was also measured.

Table 5

Summary of Study Populations and Timelines

	Age (Years)		Post-Operative		
N	*(M ± SD)*	Pre-Operative	ICU Stay	Recovery Phase	
Study 1 Transcatheter Aortic Valve Implantation (TAVI) Patients					
125	80.45 ± .5	MMSE, RBANS, Blood Chemistry	RBANS, SIRS Diagnosis, Blood Chemistry, Clinical Scores	3-Month RBANS	12-Month RBANS
Study 2 General Cardiac Surgery Patients					
224	70.02 ± .6	MMSE, Education, Blood Chemistry	SIRS Diagnosis, Delirium, Coma, Clinical Scores		6-Month telephone MMSE
Study 3 General Operative Patients (majority cardiac surgery)					
31	65.55 ± 7.9	MMSE, Blood Chemistry	SIRS Diagnosis, Blood Chemistry over several time points at ICU, Delirium, Coma, Clinical Scores	3-4 Month MMSE	6-Month MMSE, comprehensive neuropsychological test battery

Note. ICU = Intensive care unit, Recovery = after hospital release; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome.

Common Methods

The standard methods employed in all three studies are presented here.

Cognitive Assessments

The *Mini-Mental Status Examination* was used in all three studies (Folstein, 1975). This cognitive screening for dementia took approximately 10 minutes. It included 30

Items covering the following domains: orientation to time (five items, 5 pts.), orientation to place (five items, 5 pts.), memorization (three items, 3 pts.), attention (one item, 5 pts.), recall (three items, 3 pts.), naming objects (two items, 2 points), repeating a sentence (one item, 1 pt.), comprehension/praxis (three items, 3 points), reading a sentence (one item, 1 pt.), writing a sentence (one item, 1 pt.), drawing/figure copy (one item, 1 pt.). There are different cut-scores for this test, but it is generally agreed that a score below 24 may indicate dementia. A telephone variant was employed in the follow-up assessment of Study 2, which excluded eight items requiring using the hands or seeing/reading.

The *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS) was employed in Studies 1 and 2 (Randolph et al., 1998). This comprehensive neuropsychological test battery took approximately 30 minutes to administer. It was originally developed to screen dementia in adults but has been used to measure such cognitive change over time, as improvement during cognitive rehabilitation and to track change in clinical trials of dementia (Duff et al., 2008) and for identifying mild cognitive impairments (Karantzoulis et al., 2013). It was validated for people aged 12-90 years of age.

RBANS comprises 12 subtests, which measure six cognitive domains: short-term memory, retention, long-term memory, language, attention, and visuoconstruction (Randolph et al., 1998). It has been used in numerous clinical trials to measure global cognitive change. Standardized index scores for the six cognitive domains listed are corrected for age, sex, and education. A total score for overall cognitive functioning based on index scores was calculated and was expressed in Standard Values (M = 100, SD = 10). For comparison purposes, RBANS total scores and subscores were transformed using age-based norms from an American English-language normative data evaluation (Randolph et al., 1998) since German norms did not exist.

Inflammation. Different proinflammatory serum biomarkers were ascertained pre- and post-surgery, representing distinct aspects of the inflammatory process. The exact number and type of markers included varied from study to study, but there is a consistency in the use of leukocyte count and C-reactive protein across all three studies since these are gold standards in surgery and intensive care for identifying the potential an inflammatory state due to infection. The clinical meaning of each marker and pathological cut score are listed in Table 6. Names, magnitude/units, and pathological ranges (if applicable) are consistent across studies.

Across studies, for analysis purposes, there were three parameters determined for each proinflammatory serum biomarker: the "presurgery" level was used as a proxy for chronic inflammation (measured during the presurgical medical consultation and evaluation). The "peak" (maximum) level of inflammation during the post-operative period was determined from the available measurements, which varied in frequency and timing. Acute systemic inflammation was then operationalized as the simple difference between the post-operative peak score and the presurgery score and denoted "rise."

Table 6

Serum biomarker units and reference ranges

Serum Biomarker	Units	Pathological Range(s)	Clinical Meaning
C-reactive Protein (CRP)	mg/l	>3	The gold standard to detect and monitor infective diseases, with a half-life of 19h and a well-established range of increase after an inflammatory stimulus up to 100-fold and more from baseline levels.
Procalcitonin (PCT)	µg/l	<0.5	Local bacterial infection is possible, and systemic infection (sepsis) is unlikely. Minimal risk for the development of severe systemic infection (severe sepsis)
		>0.5 to <2.0	A systemic infection (sepsis) is possible, but several conditions induce PCT. Moderate risk for the development of severe systemic infection (severe sepsis).
		>2.0 to 10.0	Systemic infection (sepsis) is likely, as other reasons are unknown. There is a substantial risk of developing a severe systemic infection (severe sepsis).
		>10	Pronounced systemic inflammatory reaction, almost exclusively because of severe bacterial sepsis or septic shock. High probability of severe sepsis or a septic shock.
Interleukin-6 (IL-6)	pg/ml	*0-17 years* > 15 *18-99 years* > 5	High concentrations indicate an inflammatory process due either to activation of monocytes/macrophages after, e.g., bacterial infection, or non-immunological cells such as endothelial cells, e.g., tissue trauma or tissue hypoxia.
Interleukin-8 (Il-8)	pg/ml	0 – 99 years >15	High concentrations indicate an inflammatory process due to different causes, as for IL-6.
Leukocytes (LZ)	G/L	*18-64 years* <3.9 or >10.2 *≥65 years* <3.6 or >10.5	Too low or too high may indicate an inflammatory response, most commonly the result of infection, but may also occur following certain parasitic infections or bone tumors. It may also occur after strenuous exercise, convulsions such as epilepsy, emotional stress, pregnancy and labor, anesthesia, and epinephrine administration.
Neuron Specific Enolase (NSE)	ng/ml	>12.5	Marker of neuronal death. It is upregulated in tumor patients.
S100	µg/l	> 0.1 µg/l	Healthy persons show serum S100 concentrations below this threshold in 95% of the cases. The median is 0.04 µg/l.

Note. Source of these reference ranges and clinical designations were taken directly from the internal documents for each biomarker at University Hospital Bonn Central Laboratory's intranet website: http://www.meb.uni-bonn.de/klinbiochem/laborbuch November 27, 2016.

Assessment of SIRS. Medical doctors assessed the Systemic Inflammatory Response syndrome based on the SIRS criteria of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (ACCP/SCCM), as described in

Textbox ***1*** (Engel et al., 2007).

Other key perioperative parameters for analysis. The demographic information age, education (if available), history of stroke, diabetes, and other comorbidities were included. Further, surgery-related parameters, such as type of surgery, and duration of surgery, were assessed.

Statistics and data analysis. Statistical tests were performed in SPSS 22.0. Across studies, the α-level for most tests used was 5%. Inflation of Type-1 error was reduced in cases of multiple testing using a Holms correction (Blakesley et al., 2009). A dummy variable to measure SIRS (1 for SIRS, 0 for no SIRS) was created, along with dummy variables for pathological versus not pathological cytokine scores (1 for pathological, 0 for normal). Pearson Chi-Square tests were conducted for frequency differences between groups (SIRS versus Non-SIRS) and ordinal data of descriptive parameters. Independent samples of student t-tests with 2-sided significance were conducted for continuous descriptive data. Bivariate Kendall's Tau correlation analyses were conducted for cognitive and inflammatory parameters since normality could not always be assumed. Hierarchical regression analyses were also employed to analyze biological markers of inflammation on cognitive parameters in cases of one-shot cognitive assessments to examine individual biomarkers pre- and post-surgery and dynamic change (rise) of the biomarker measures. Nested parameters using repeated measures were analyzed using Multilevel Modelling with Repeated Measures (MMRM).

Study 1. Transcatheter Aortic Valve Implantation Patients

This retrospective analysis is based on a longitudinal dataset collected from January 2008 to June 2011, whose primary aim was to assess the safety of a minimally invasive cardiac surgery procedure called TAVI (Ghanem et al., 2013; Sinning et al., 2013). Both mortality and possible impairments in cognition were assessed. The first study data analysis indicated that those diagnosed with SIRS had a higher mortality risk. Further, cognitive performance prior to surgery was impaired in patients on average by about one standard deviation below norms, which dipped and by one year returned to baseline levels in some, but not in all patients (Ghanem et al., 2013). This research represents the first comparison of inflammation and cognition in this study cohort.

Hypotheses

The main questions were posed in this study were:

Hypothesis 1: Are higher chronic inflammation levels associated with acute inflammation indicators?

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance at any time point?

Hypothesis 3: Do chronic and acute systemic inflammation influence the *trajectory* of cognitive performance over time?

Hypothesis 4: Is there an interaction between chronic and acute inflammation on cognitive performance?

Specifically, Study 1 examined relationships between a broad range of well-established and closely monitored inflammatory biomarkers and a composite (total) score of a well-known and established neuropsychological test battery (RBANS). Multilevel modeling was employed to analyze the effects of specific inflammatory biomarkers on cognition over four cognitive assessments for a year.

Methods

Recruitment. All patients scheduled for transcatheter aortic valve implantation due to severe, symptomatic aortic stenosis and high or prohibitive operative risk between October 2009 and December 2010 were sequentially screened at the Department of Medicine/Cardiology at the University Hospital Bonn for inclusion in this study.

Inclusion criteria were a) severe, symptomatic aortic stenosis with or without regurgitation and high or excessive peri-operative risk, b) echocardiographic aortic valve annulus diameter >20 and <27 mm, and c) diameter of the ascending aorta <45 mm.

Exclusion criteria consisted of permanent pacemaker implantation, claustrophobia, or hemodynamic instability impeding transport, hypersensitivity or contraindication to post-interventional dual platelet inhibition; sepsis or active endocarditis; bleeding diathesis or coagulopathy; recent cerebrovascular accident; mitral or tricuspid valvular insufficiency (>grade II); left ventricular or atrial thrombus; previous aortic valve replacement; progressive disease with life expectancy <1 year, and inability to give written informed consent. Those with a non-autarkic lifestyle or a psychiatric disorder were excluded. The study protocol was approved by the local institutional review board and followed the Declaration of Helsinki guidelines. Written informed consent was obtained from all patients.

Ethical Considerations.

This study protocol was reviewed by the Medical Ethics Review Board of the University Hospital Bonn (IRB Number 255/08) under the title “Incidence and Severity of Silent and Apparent Cerebral Embolism After Conventional and Minimal-invasive Transfemoral Aortic Valve Replacement.” The study was conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for Good Clinical Practice and the

relevant national regulations and the Declaration of Helsinki, as laid out in the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 ("Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use," 2002).

This study is registered at the International Clinical Trials Registry Platform of the U.S. National Library of Medicine "ClinicalTrials.gov" (primary registry trial identifier: NCT00883285; first registration date: April 17, 2009, cross-referenced at the World Health Organization International Clinical Trials Registry Platform). The study was sponsored by the University of Bonn Medical Center and conducted under Prof. Claas P. Naehle, Assistant Professor of Radiology at the University of Bonn Medical Center.

TAVI Surgery. TAVI was performed in spontaneously breathing patients in deep sedation. A balloon catheter was used to deliver the valve replacement to the left ventricle passing through the aortic valve (Third generation CoreValve® revalving system, Medtronic Inc., USA). The details of this surgery have been published previously (Ghanem et al., 2013).

Cognitive Assessments. Before surgery, the Mini-Mental Status Examination (Folstein, 1975) was conducted by staff medical doctors. Repeated assessments before surgery, at three days, three months, and 12 months post-surgery, were conducted using the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS; Randolph et al., 1998).

Proinflammatory Serum Biomarkers. Blood draws needed to determine cytokines and leukocytes were taken at baseline and at 1 hour, 4 hours, 24 hours, 48 hours, 72 hours, and seven days. Proinflammatory cytokines [interleukin-6 (IL-6) and interleukin-8

(IL-8)], as well as acute phase reactants [C-reactive protein (CRP), procalcitonin (PCT)] and Leukocyte count (LZ), were measured at baseline and at several time points after surgery while patients were monitored at the intermediate intensive care unit. High sensitive C-reactive protein (CRP) levels were determined nephelometrically (hsCRP Flex reagent cartridge, Dimension Vista System, Siemens Healthcare Diagnostics GmbH, Munich, Germany), the advantage being that the sensitivity even at low levels of CRP is high. PCT was determined via immunoluminometric assay (Liaison Brahms PCT, DiaSorin S.p.A., Saluggia, Italy). IL-6 and IL-8 were assessed with the help of an immunoluminometric sandwich assay (IL-6 and IL-8 Immulite Test, Siemens Healthcare Diagnostics GmbH, Munich, Germany). Leucocyte count was conducted via fluorescence flow cytometry and electrical impedance (Sysmex XE-2100, Kobe, Japan; Sinning et al., 2013).

Demography, comorbidities, perioperative parameters. Age, sex, body-mass index, smoking status, diabetes, hypertension, atrial fibrillation, hemodialysis, prior myocardial infarction, coronary artery disease, prior CABG, and SIRS Diagnosis were assessed. In addition, the ejection fraction (EF), a measurement of heart failure which indicates the percentage of blood in the left ventricle pumped out at each contraction, was assessed and included as a fixed effect in the cognitive data analysis since it represents a significant potential confounder. Time of procedure duration and assessment of SIRS while in intermediate care was assessed.

Statistics and data analysis.

Missing data analysis. Missing value analysis was conducted using SPSS 22.0, as recommended in (Barbara Tabachnick & Linda Fidell, 2007), including estimation of means and t-tests and evaluations of the pattern of missing data. The specific SPSS Output of the results of these analyses is included in Appendix B. This analysis revealed

that missing values were more likely in the SIRS group in the follow-up visits evaluating cognition. (See Appendix B). Estimation of means analysis failed to converge in 25 iterations, and Little's MCAR test was nonsignificant ($\chi^2_{(df: 35)} = 43.972$, $p = .142$); it also failed to converge in 100, 150, and 200 iterations (indicating that data was missing completely at random).

However, an investigation of whether specific missing data depended on earlier observations of the outcome variable was warranted, i.e., whether missing cognitive biomarker data depended on pre-operative cognition or biomarker data or SIRS criteria. Next, the question was raised as to whether specific covariates, such as sex, age, and premorbid cognitive ability, were related to missing data, i.e., were males more likely to have missing data than females? To make a distinction between ignorable missing data (i.e., those not dependent on observations of the outcome variable or covariates and non-ignorable data, i.e., missing dependent on the earlier observation of covariates) an independent sample 2-sided t-test for continuous and a 2-sided Pearson chi-square test for dichotomous and categorical data was carried out based on a dummy variable (Twisk, 2013).

Dealing with missing data. For correlational analysis, missing values were handled with multiple imputations for maximally 10% of missing values using means. The later analyses using multilevel modeling used only real data, with no imputed values.

Tests of normality. Kolmogorov-Smirnov testing of normality of the cognitive raw data revealed that MMSE pre-op ($D(125) = .162$, $p < .001$) and RBANS at 3 months ($D(110) = .094$, $p = .018$) were non-normal for ungrouped data (See Appendix B, "Testing of Normality"). Kolmogorov-Smirnov testing of normality of serum biomarkers revealed that 4 of the 5 Biomarkers were also nonnormal (Peak PCT: $D(123) = .394$, $p < .000$; Peak IL-6: $D(123) = .412$, $< .001$; Peak IL-8: $D(123) = .339$, $p < .001$; Peak Leukocytes:

$D(123) = .469, < .001$). Since the sample sizes were rather large, no further attempts at transformation or reduction of outliers were undertaken (A. Field, 2013).

Correlation Analysis. Bivariate Pearson correlation of cognition and biomarker data, chi-square tests of frequency and ordinal data, and independent sample 2-sided student T-Tests were conducted for continuous descriptive data.

Multilevel modeling with repeated measures. Hierarchical linear mixed-effects models were employed, also known as multilevel modeling with repeated measures (MMRM). This type of modeling enabled the evaluation of the association of SIRS and proinflammatory serum biomarkers on cognition over time. Due to the nonindependence of individual observations of cognition and the nested structure of the data, the assumption of independent residuals would not hold; hence, linear regression would not have been appropriate. Further, due to missing data depending on the diagnosis of SIRS, there was a need to handle meaningful missing data. MMRM also enables estimation of data outcomes if subjects had not dropped out of the study, like Multiple Imputation, baseline data, and modeling the growth over time. For MMRM analysis, only real data was used since missing data does not affect the validity of the results.

MMRM was used to account for the nested structure of data with the outcome measure (cognition) being repeatedly measured in the same person, the person also being located within a higher-level group, such as diagnosis of SIRS or level of pro-inflammatory serum biomarker. A 3-level model was used with RBANS as level-1 repeated measures, individual participants as level-2, and inflammatory parameter as level-3 (see an example using SIRS diagnosis in Figure 4).

Fixed effects of proinflammatory serum parameter and time (as a categorical variable, with the last assessment as the reference time point) and the interaction between inflammatory parameter and time were evaluated. Further, moderation effects for chronic

and acute inflammation were investigated using MMRMs by entering interactions between chronic and acute with interaction terms.

$$\boldsymbol{Y_{ijk} = \beta_0 + \beta_1 Time + \beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_p X_p + u_{oi} + u_{1ik} Time_{1j} + u_{ok} + u_{1k} Z_k + \varepsilon_{ijk}} \quad (0)$$

Equation 1 represents a model for the three-level model, where Y_{ijk} represents the set of RBANS scores, where the following definitions hold:

β_0 is the mean of the RBANS score,

$\beta_1 Time$ represents the fixed effect time,

$\beta_2 X_2 + \beta_3 X_3 + \cdots + \beta_p X_p$refer to the individual RBANS scores (*i*),

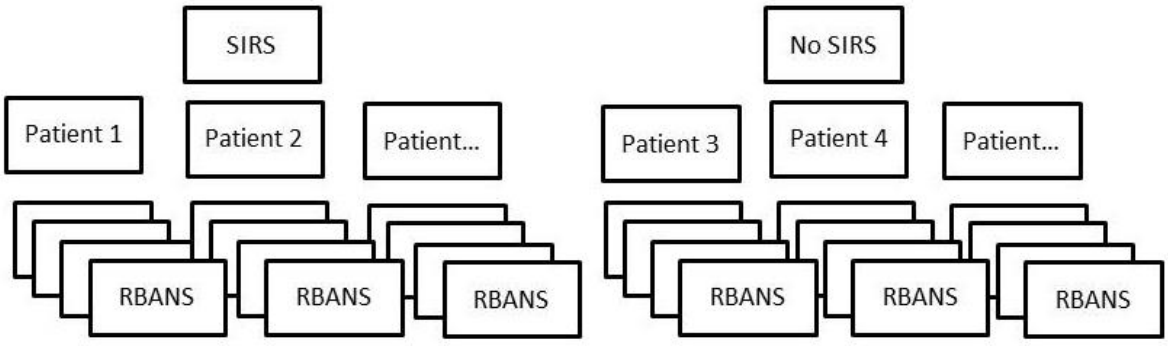
$u_{oi} + u_{1ik} Time_{1j}$ refers to the individual patient (*j*),

$u_{ok} + u_{1k} Z_k$ refers to the proinflammatory biomarker (*k*)

ε_{ijk} is a residual term indicating outcome level error.

Figure 4

Three-level MMRM with patients, SIRS, and repeated cognitive measures



Note. Here, SIRS diagnosis as a predictor of cognition is measured by RBANS over four assessment points, with time as a categorical variable. This basic structure is used for all models using MMRM with the continuous serum proinflammatory biomarkers as predictors.

Alternative underlying matrix structures made the most theoretical sense and best fit according to the Akaike information criterion (AIC). An unstructured (UN) variance-covariance structure for the Sigma matrix was selected for all models used.

A single model was conducted for SIRS diagnosis, which included interaction with time term. For each proinflammatory biomarker, separate multilevel models with repeated measures were conducted for presurgery (Model 1), rise (Model 2), and peak values (Model 3). Two further models were analyzed, including both presurgery and rise levels simultaneously (Model 4), to evaluate their differential influence of presurgery and rise in biomarker post-surgery. Further, a combined analysis of presurgery and rise with an interaction term presurgery*rise was conducted (Model 5). A goodness of fit comparison using the AIC measure was possible only between Models 4 and 5 because they are essentially nested models. This measure is not useful, however, for comparing across distinct models.

Further, the potential confounding effect of ejection fraction indicating heart failure was examined by adding it to each model.

Intraclass Correlation Coefficients. An Intraclass Correlation Coefficient (ICC) for subject performance in RBANS scores over time was calculated to indicate how consistent individuals were over time, calculated based on covariance over variance for the parameter estimates of subject intercept (Residuals) for each model.

Results

Descriptive results. Continuous and frequency data are shown in Table 7 and Table 8. Age, length of stay in the hospital, and BMI did not differ between those with and without SIRS. Length of ICU stay and surgery were considerably longer for those

diagnosed with SIRS. Those with SIRS also had lower pre-operative MMSE scores, greater acute kidney injury frequency, and more frequent mortality.

Table 9 shows the scores of RBANS at each assessment point in standard values and proinflammatory markers presurgery (baseline), at the peak level in the seven days post-surgery, as well as for the difference between baseline and peak, indicative of acute inflammation and SIRS diagnosis as an indicator of acute inflammation. The average RBANS score for the entire group was approximately two standard deviations below the expected norm prior to surgery.

Table 7

Continuous patient and clinical characteristics by SIRS diagnosis

	Total Group			*No SIRS*			*SIRS*							*95% CI*		
Parameter	*N*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*LL*	*UL*	*Sig.*
Age (years)	125	80.45	.550	82	80.73	.658	42	79.67	.989	0.918	122	1.07	1.160	-1.23	3.36	.360
LOS Hospital (days)	117	18.62	1.558	77	15.51	1.550	40	24.60	3.271	-2.512	57.0	-9.094	3.620	-16.34	-1.84	.015*
LOS ICU (days)	92	5.68	1.170	64	3.37	.248	28	10.96	3.653	-2.073	27.2	-7.59	3.661	-15.09	-.08	.048*
BMI	124	26.13	.521	81	26.40	.649	42	25.59	.902	0.733	121	0.81	1.110	-1.38	3.01	.465
Surgery (Minutes)	113	89.46	3.845	72	83.72	4.512	40	100.03	6.983	-2.043	110	-16.30	7.981	-32.11	-.48	.043*
EF (%)	125	55.82	1.462	82	59.83	1.642	42	53.85	2.949	0.883	67.0	2.98	3.375	-3.75	9.71	.380
MMSE (max. 30)	125	25.30	.317	82	26.13	.317	42	23.64	.645	3.468	61.4	2.49	.718	1.055	3.92	.001**

Note. Independent Samples Test, 2-sided significance, equal variances assumed, alpha-level = .05. SIRS = Systemic Inflammatory Response Syndrome; LOS = Length of Stay; ICU = Intensive Care Unit; BMI = Body Mass Index; EF = Ejection Fraction, MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$. ** $p < .01$.*

Table 8

Sample and clinical characteristics by SIRS diagnosis via Pearson Chi-square tests

	Total			No SIRS			SIRS					
Parameter	*N*	*Freq.*	*%*	*n*	*Freq.*	*%*	*n*	*Freq.*	*%*	*df*	χ^2	*Sig.*
Sex (male)	125	66	52.8%	82	44	53.7%	42	22	52.4%	1	.018	.893
Mortality	125	40	32.0%	82	20	24.4%	42	19	45.2%	1	5.599	.018*
Previous Stroke	125	23	18.4%	82	12	14.6%	42	11	26.2%	1	2.455	.117
Diabetes	125	38	30.4%	82	28	34.1%	42	10	23.8%	1	1.396	.305
Atrial Fibrillation	125	47	37.6%	82	28	34.1%	42	17	40.5%	1	.179	.699
Aortic Regurgitation post OP:	-	-	-	-	-	-	-	-	-	2	1.772	.412
Mild	125	61	48.8%	82	43	52.4%	42	18	42.9%	-	-	-
Moderate	125	10	8.0%	82	5	6.1%	42	5	11.9%	-	-	-
Acute Kidney Injury	124	26	20.0%	82	6	7.3%	42	16	38.1%	1	11.243	.002**

Note. Chi-square homogeneity test for categorical data by SIRS status; asymptotic significance testing; cases were excluded test-by-test for missing data. SIRS = Systemic Inflammatory Response Syndrom; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$. ** $p < .01$.*

Table 9

Descriptive statistics ungrouped and according to SIRS diagnosis

	Total					No SIRS			SIRS								
Parameter	*N*	*Min*	*Max*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*95% CI LL*	*95% CI UL*	*Sig.*
RBANS																		
Presurgery	125	44	129	81.47	1.36	82	83.30	1.46	42	78.21	2.80	1.609	64.05	5.09	3.16	-1.22	11.41	.113
3d post-op	110	41	135	85.50	1.65	78	87.09	1.83	32	81.63	3.49	1.506	108	5.46	3.63	-1.73	12.66	.135
3m post-op	104	47	126	83.17	1.50	75	83.97	1.67	29	81.10	3.26	0.852	102	2.87	3.36	-3.80	9.55	.396
12m post-op	97	47	120	83.70	1.53	71	84.61	1.66	26	81.23	3.51	0.973	95	3.37	3.46	-3.50	10.26	.333
CRP (mg/l)																		
Presurgery	125	0.20	199	14.82	2.39	82	12.85	2.06	42	18.91	5.86	0.437	121	.01	.016	-0.02	0.03	.663
Rise	125	0.00	239.30	69.20	3.94	82	61.95	3.68	42	84.97	8.71	-1.382	61.92	-.74	.536	-1.81	.33	.172
Peak	125	1.0	240	84.02	4.18	82	74.80	4.13	42	103.89	8.63	-1.363	61.81	-.73	.539	-1.81	.34	.178
PCT (µg/l)																		
Presurgery	123	0.02	.81	0.09	.00	81	0.09	.01	42	0.09	.01	-0.976	51.43	-6.07	6.21	-18.54	6.40	.334
Rise	123	0.00	13.11	0.81	.22	81	0.55	.23	42	1.30	.48	-2.432	56.05	-23.02	9.46	-41.97	-4.05	.018*
Peak	123	0.05	13.13	0.90	.22	81	0.65	.24	42	1.38	.48	-3.038	60.31	-29.08	9.57	-48.23	-9.93	.004**

Table continues

Table 9

Descriptive statistics ungrouped and according to SIRS diagnosis (continued)

	Total					No SIRS			SIRS								
Parameter	*N*	*Min*	*Max*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*95% CI*		*Sig.*
																LL	*UL*	
IL-6 (pg/ml)																		
Presurgery	123	0.50	179	13.97	2.10	81	14.43	2.72	42	13.06	3.23	.308	121	1.37	4.44	-7.43	10.18	.758
Rise	123	0.00	7471.20	137.75	60.66	81	57.24	5.91	42	293.02	176.29	-1.337	41.09	-235.78	176.38	-591.92	120.42	.189
Peak	123	2.20	7474	151.71	60.64	81	71.67	6.70	42	306.08	176.05	-1.331	41.11	-234.40	176.17	-590.17	121.36	.191
IL-8 (pg/ml)																		
Presurgery	123	5.00	45.90	14.74	.75	81	15.23	1.07	42	13.80	.72	1.100	120.50	1.42	1.29	-1.14	3.99	.273
Rise	123	0.00	589.50	27.38	7.23	81	21.34	7.43	42	39.01	15.61	-1.159	121	-17.66	15.24	-47.84	12.51	.249
Peak	123	7.60	604.00	42.12	7.27	81	36.58	7.45	42	52.81	15.73	-1.059	121	-16.23	15.33	-46.59	14.11	.292
Leukocytes (G/L)																		
Presurgery	122	2.33	17.64	7.09	.19	80	6.71	.18	42	7.81	.41	-2.446	57.914	-1.09	.44	-1.99	0.45	.017*
Rise	122	0.00	1013.12	12.48	8.27	80	15.51	12.63	42	6.72	.67	0.503	120	8.79	17.47	-25.80	17.47	.616
Peak	123	3.21	1022.00	19.48	8.22	81	22.06	12.50	42	14.52	.68	0.433	121	7.53	17.40	-26.92	17.40	.666

Note. These values are based on real scores. Independent Samples Test, 2-sided significance, equal variances not assumed, alpha-level = .05. Presurgery refers to assessment prior to surgery. Peak refers to the maximum cytokine value seven days post-surgery. "Rise" = difference between Peak and Presurgery levels, a measure of acute systemic inflammatory response. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; IL = Interleukin; PCT = Procalcitonin; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$. ** $p < .01$.*

Scores improved somewhat at the second RBANS assessment, but they returned to the baseline level at the three-month and 12-month assessments. At any given time, the RBANS scores for the SIRS group were lower than those of the non-SIRS group, but not statistically significantly, primarily due to the considerable variation of scores in the SIRS group.

The frequency of pathological values at baseline and peak are shown in Table 10. Two-thirds of patients had pathologically high CRP and IL-6 values prior to surgery. In contrast, PCT, IL-8, and leukocytes were mainly normal across patients at baseline. After surgery, most patients had a pathological peak value for CRP, IL-6, and IL-8. The frequency of pathological value of PCT using the three different cut-scores yielded different results. Only for the medium-level cut-score was there a meaningful shift from baseline to 22.4% pathological compared to 0% before surgery. Leukocyte levels resolved quickly and were not pathological after surgery.

Table 10

Pathological status at baseline and peak of inflammatory biomarkers

	Baseline			Peak		
Inflammatory Biomarker	Normal *Freq. (%)*	Pathological *Freq. (%)*	Missing *Freq. (%)*	Normal *Freq. (%)*	Pathological *Freq. (%)*	Missing *Freq. (%)*
CRP	48 (38.4%)	77 (61.6%)	0 (0%)	3 (2.4%)	122 (97.6%)	0 (0%)
PCT_{Low}	119 (95.2%)	6 (4.8%)	0 (0%)	122 (97.6%)	1 (0.8%)	2 (1.6%)
PCT_{Medium}	123 (98.4%)	0 (0%)	2 (1.6%)	97 (77.6%)	28 (22.4%)	0 (0%)
PCT_{High}	123 (98.4%)	0 (0%)	2 (1.6%)	115 (92.0%)	10 (8.0%)	0 (0%)
IL-6	39 (31.2%)	84 (67.2%)	2 (1.6%)	1 (0.8%)	124 (99.2%)	0 (0%)
IL-8	80 (64.0%)	43 (34.4%)	2 (1.6%)	32 (25.6%)	93 (74.4%)	0 (0%)
LZ	113 (90.4%)	9 (7.2%)	3 (2.4%)	122 (97.6%)	0 (0%)	3 (2.4%)

Note. Cut scores for PCT indicate low (> 0.5 µg/l), moderate (>2.0 µg/l), and high (>10 µg/l) likelihood of systemic infection. Cut-scores for IL-6 and LZ were age-based. The LZ had lower and upper cut-points, which were accounted for in the calculation.CRP = C-reactive Protein; PCT = Procalcitonin; IL = Interleukin; LZ = Leukocyte Count.

Correlation Analyses. A correlation analysis displayed in Table 11 includes cognitive scores, inflammatory cytokines, leukocytes, and SIRS diagnosis. RBANS scores correlated positively with each other across time assessment points. The presurgery RBANS score did not correlate with any proinflammatory biomarker level. The 3-day post-surgery RBANS correlated negatively with peak CRP level, peak leukocyte, and baseline and peak IL-6 levels. The 3-month post-surgery RBANS correlated negatively with CRP peak and baseline and peak PCT levels. The 12-month post-surgery RBANS score correlated negatively with baseline PCT level.

No RBANS score correlated with the diagnosis of SIRS using Pearson correlation. In contrast, MMSE score presurgery correlated negatively with the diagnosis of SIRS and with peak leukocyte level after surgery, despite the peak leukocyte levels post-surgery being non-pathological.

Cytokine levels before surgery did not correlate with post-surgery SIRS diagnosis. On the other hand, leukocyte levels prior to surgery did correlate positively with SIRS. Post-surgery cytokine peaks for CRP, IL-6, and Leukocytes correlated positively with SIRS diagnosis. In addition, the change from baseline-to-peak parameter correlates positively with SIRS for CRP, IL-6, IL-8, and Leukocytes, as shown in Table 11.

Regarding associations between baseline and peak levels of the same cytokine, correlation analysis yielded the lowest correlation for IL-6 between baseline and peak levels (r = .271), with CRP having a moderate correlation (r = .319), as had PCT (r = .330). IL-8 was higher (r = .510), and LZ values at baseline and peak had the highest level of association (r = .521).

Table 11

Bivariate correlation analysis of cognitive and serum biomarker parameters

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
1. SIRS (2 or more Criteria)	--													
2. MMSE presurgery	-.324**	--												
RBANS														
3. presurgery	-.159	.494**	--											
4. 3 days post-op	-.142	.441**	.728**	--										
5. 3 months post-op	-.105	.471**	.765**	.795**	--									
6. 12 months post-op	-.107	.455**	.814**	.836**	.954**	--								
CRP														
7. Presurgery	.016	-.134	-.172	-.139	-.159	-.170	--							
8. Peak	.256**	-.172	-.172	-.189*	-.226*	-.164	.319**	--						
9. Rise	.193*	-.052	-.053	-.124	-.142	-.070	-.057	.831**	--					
PCT										--				
10. Presurgery	.001	-.133	-.076	-.127	-.199*	-.188	.203*	-.059	-.227*					
11. Peak	.108	-.031	-.105	-.096	-.219*	-.179	.154	.416**	.307**	.330**	--			
12. Rise	.192*	.034	-.048	-.055	-.102	-.072	.044	.444**	.435**	-.166	.791**	--		
IL6														
13. Presurgery	-.083	-.003	-.164	-.206*	-.097	-.144	.529**	.075	-.153	.089	.122	.099	--	
14. Peak	.241**	-.118	-.154	-.223*	-.133	-.070	.217*	.590**	.498**	-.008	.432**	.445**	.271**	--
15. Rise	.260**	-.076	-.075	-.174	-.087	-.017	.077	.555**	.585**	-.061	.432**	.472**	.014	.909**

Table continues

Table 11

Bivariate correlation analysis of cognitive and serum biomarker parameters (continued)

Variable	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
IL8																				
16. Presurgery	.057	.178	-.020	-.030	-.028	.019	.166	-.081	-.138	.173	.148	.069	.172	.089	.050	--				
17. Peak	.106	.062	.058	-.026	.027	.095	.120	.202*	.154	.120	.292**	.282**	.103	.425**	.391**	.510**	--			
18. Rise	.188*	-.098	-.044	-.084	-.080	-.034	.018	.335**	.323**	.039	.300**	.327**	.036	.420**	.428**	-.162	.659**	--		
LZ																				
19. Presurgery	.227*	-.178	-.129	-.214*	.024	-.090	.278**	.026	-.105	.044	-.135	-.130	.243**	-.035	-.103	-.009	-.058	-.040	--	
20. Peak	.550**	-.231*	-.152	-.266**	-.110	-.175	.110	.225*	.183	-.071	.186	.265**	.114	.288**	.259**	.095	.059	.097	.521**	--
21. Rise	.483**	-.126	-.035	-.152	-.078	-.084	-.050	.222*	.290**	-.112	.295**	.428**	-.039	.339**	.396**	.107	.100	.144	-.021	.782**

Note. Bivariate correlation analysis. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; PCT = Procalcitonin,; IL = Interleukin; LZ = Leukocyte Count.

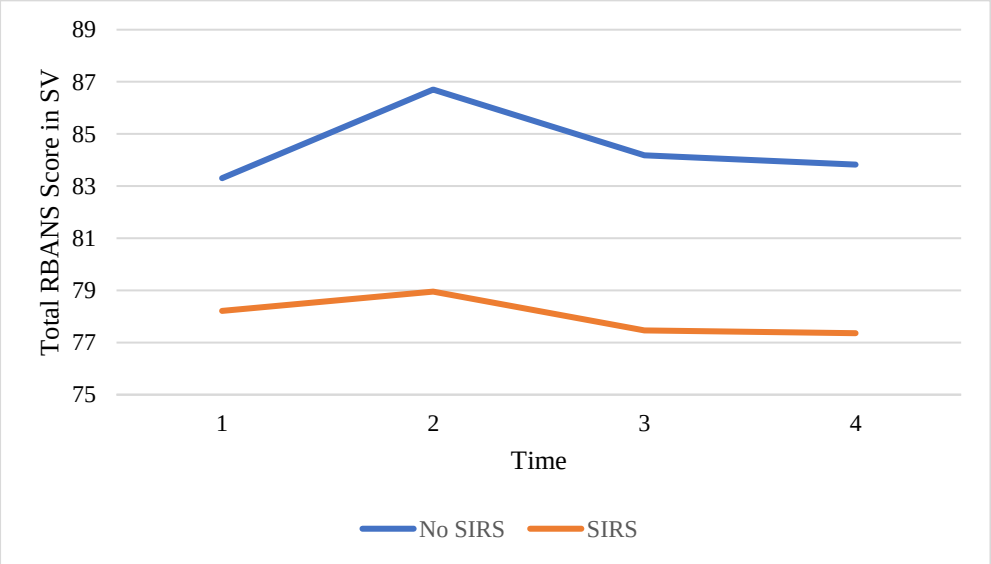
** $p < .05$. ** $p < .01$. *** $p < .001$.*

Multilevel Modeling with Repeated Measures (MMRM). Using the smallest Akaike information criterion (AIC) to compare 15 variance-covariance matrix structures for Sigma, an unstructured correlations (UNR) structure was considered the best fit for each of the models calculated. Results of these analyses for SIRS and each proinflammatory serum biomarker are bundled in the tables below.

Diagnosis of SIRS. MMRM analysis included SIRS, time, sex, age, and EF as independent variables, whereas SIRS, time, their interaction, sex, age, and EF were designated fixed effects. This analysis yielded a main effect of SIRS diagnosis (p = .033), but no main time effect (p =.156) or interaction of SIRS with time (p = .681), and no fixed effect of sex (p = .805), age (p =.737) or EF (p = .244). Figure 5 graphically depicts this for RBANS scores over time as estimated by MMRM for SIRS and non-SIRS. There is an approximate 6.5-point difference between the groups at any given time.

Figure 5

RBANS Score over Time by SIRS using MMRM estimates of means



Note. These analyses include age, sex, and EF as fixed effects. EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; SV = Standard Values.

Hence, no decline over time occurred due to SIRS occurrence from baseline over 12 months. Before surgery, the general level of cognition was worse among those who developed SIRS. Hence, SIRS does not modulate the course of the cognitive trajectory. The magnitude of the effect of SIRS diagnosis can be taken from the parameter estimate shown in Table 12. It should be noted that the reference category for this analysis was patients without a diagnosis of SIRS; for those with a SIRS diagnosis, there are 6.5 fewer points in the RBANS score at any given time point.

Table 12

Summary of estimates of fixed parameters MMRM analysis of SIRS as a predictor of RBANS

						95% CI	
Model	*Estimate*	*Std. Error*	*df*	*t*	*Sig.*	*LL*	*UL*
No SIRS	6.52	3.096	120.76	-2.106	.037*	-12.65	.39

Note. These are fixed-parameter estimates for the main effect of the cytokine level. Diagnosis of "No SIRS" is the reference category, i.e., a diagnosis of SIRS yields estimated RBANS scores approximately 6.5 points below those in the group with no SIRS. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

C- Reactive Protein. The results of the Type III tests of fixed effects for each of the five MMRM analyses using CRP presurgery, rise or peak values are given in Table 13, including the interaction with time, denoted "change over time," as well as the goodness of fit measure AIC for Model 4 and 5 for purposes of comparison.

Table 13

Summary of main effects of MMRM analyses of CRP predictors of RBANS

	Main Effect	Change over Time	
Model	*Sig.*	*Sig.*	
1. Presurgery	.068	.984	
2. Rise	.074	.128	
3. Peak	.007**	.133	
4. Combined			AIC
Presurgery	.026*	.877	**3193.578**
Rise	.027*	.104	
5. Combined with interaction term			
Presurgery	.220	.878	3204.114
Rise	.112	.111	
Presurgery x Rise	.334		

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 4 RBANS assessments. These analyses include age, sex, and EF as fixed effects. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CRP = C-reactive Protein; AIC = Akaike information criterion.

** $p < .05$. ** $p < .01$.*

The presurgery CRP (Model 1) showed no main effect of CRP, change over time, age, sex, or EF. The addition of age, sex, and EF interaction terms with time did not change this pattern of results. Rise had no main effect and no change over time, although time itself had a main effect (Model 2). Neither age, sex, nor EF had main effects or interaction with time (data not shown). Peak CRP had a main effect, as did time itself (p = .018), but there was no change over time. Neither age, sex, nor EF had main effects. The same analysis with interaction terms for age, sex, and EF showed essentially the same pattern of results, although their inclusion weakened the main effect of time so that it was no longer significant *(p* = .162), and the main effect of CRP was strengthened *(p* = .008).

The entry of both presurgery and rise in CRP in the same model (Model 4) yielded a main effect of both parameters and a fixed effect of time *(p* = .015), but no main effect of age, sex, EF, or change over time. This model also had the best fit of any model analyzed, according to the smallest AIC. Model 5, which included an interaction term between presurgery and rise levels, yielded no significant interaction effect and negated the main effects of either presurgery or rise CRP. A further calculation, including change over time for the interaction term presurgery CRP x rise CRP, had a worse fit and no effect (data not shown).

The parameter estimates of each model are reported in Table 14 and estimate the influence on cognition at any given time point over the four assessments during the 12-month study period. Hence, for the highly significant CRP peak in (Model 3), a 100 mg/L increase in CRP peak means 7.5 fewer points in RBANS total score at any assessment point. There was no “decline” but a generally lower cognitive performance level here.

Likewise, in Model 4, CRP presurgery increases by 100 mg/L points, indicating 11.2 fewer points in RBANS score at any given assessment point. The parameter estimate for CRP rise in Model 4 indicates that a 100 mg/L increase means 6.7 fewer points in the

RBANS score at any assessment point. For CRP, both presurgery level and rise were associated with fewer points in the RBANS score. Model 4 also had the smallest AIC, indicative of a better model fit than Model 5, which included an interaction term between presurgery and rise levels. Hence both presurgery and rise values are indicators of generally worse cognitive performance but not of decline over time. There appears to be no interaction between presurgery and rise levels.

Table 14

Summary of estimates of fixed parameters MMRM Analyses of CRP predictors on RBANS

Model	*Estimate*	*SE*	*df*	*T*	*Sig.*	*95% CI*	
						LL	*UL*
1. Presurgery	-0.091	.054	112.916	-1.679	.096	-0.198	0.016
2. Rise	-0.053	.034	128.586	-1.556	.122	-0.121	0.014
3. Peak	-0.075	.031	124.684	-2.395	.018*	-0.137	-0.013
4. Combined							
Presurgery	-.112	.055	112.674	-2.042	.043*	-0.220	-0.003
Rise	-.067	.034	126.697	-1.935	.055	-0.135	0.002
5. Combined with inter-action term							
Presurgery	-.074	.067	120.250	-1.107	.270	-0.207	0.059
Rise	-.052	.037	139.448	-1.364	.175	-0.126	0.023
Presurgery x Rise	-.001	.001	116.454	-.970	.334	-0.004	0.001

Note. The main analysis includes fixed parameter estimates based on REML with age, sex, and EF. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CRP = C-reactive Protein; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$.*

Procalcitonin. As shown in

Table 15, there was no presurgery or post-surgery PCT effect over time, time itself (*p* = .438; Model 1), age, sex, or EF. The inclusion of interaction of age, sex, and EF with time did not change this pattern of results. Model 2 showed an almost significant PCT rise and a main effect of time (*p* = .043), but no change over time, no age, sex, or EF effects. The inclusion of their interaction with time nullified the significant main effect of time (*p* = .151) but otherwise showed no change in the pattern of results. In the case of Model 3, there was an almost significant change over time and a main effect of time (*p* = .038).

For the combined analysis (Model 4), there was a nearly significant effect of rise but no interaction with time. In this model, presurgery CRP level had no effect. There was no main effect of time (*p* = .307), age, sex, or EF. The inclusion of interaction with time for these latter parameters generally maintained this pattern of results, except that PCT rise was weakened (*p* = .141). In the last model (Model 5) with the interaction term presurgery*rise, no effects were found, including a lack of a main effect of time (*p* = .310). The inclusion of change over time for the interaction term (time*presurgery*rise) did not change the pattern of results and was not significant. Model 5 did have a slightly better model fit compared with Model 4.

Table 15

Summary of main effects of MMRM analyses of PCT predictors of RBANS

Model	Main Effect *Sig.*	Change over Time *Sig.*	
1. Presurgery	.112	.539	
2. Rise	.054	.186	
3. Peak	.022*	.077	
4. Combined			AIC
Presurgery	.139	.610	3108.783
Rise	.066	.222	
5. Combined with interaction term			
Presurgery	.129	.610	**3103.385**
Rise	.141	.219	
Presurgery x Rise	.706		

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 4 RBANS assessments. . Age, sex, and EF were included as main effects. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status: SIRS = Systemic Inflammatory Response Syndrome; PCT = Procalcitonin; AIC = Akaike information criterion.

* $p < .05$.

As displayed in Table 16, fixed parameter estimates revealed almost significant parameter estimates for the presurgery PCT level (Model 1). For PCT Rise (Model 2), even a ten µg/l increase means approximately 12 fewer points in RBANS at any given time point. Model 3 revealed that peak PCT increase of 10 µg/l would mean 7.8 fewer

points in RBANS at any time point. The interaction term with time did not quite reach significance.

The combined model (Model 4) revealed no significant parameter estimate for presurgery PCT. Further, it showed that a ten µg/l increase in PCT rise indicates 11.6 fewer points in RBANS level at any measurement point, although the main effect failed to reach significance (Table 16). Model 5, with the inclusion of the interaction term, yielded no significant parameter estimates, despite having the best model fit.

Table 16

Summary of estimates of fixed parameters of MMRM analyses of PCT predictors of RBANS

Model	*Estimate*	*SE*	*Df*	*T*	*Sig.*	*95% CI*	
						LL	*UL*
1. Presurgery	-34.780	18.278	139.747	-1.903	.059	-70.917	1.357
2. Rise	-1.227	.588	121.389	-2.085	.039*	-2.391	-0.062
3. Peak	-.784	.356	109.835	-2.200	.030*	-1.489	-0.078
4. Combined							
Presurgery	-32.325	18.113	139.013	-1.785	.076	-68.138	3.487
Rise	-1.163	.583	120.147	-1.996	.048*	-2.317	-0.009
5. Combined with interaction term							
Presurgery	-33.994	18.701	139.591	-1.818	.071	-70.968	2.981
Rise	-1.413	.882	122.262	-1.602	.112	-3.159	0.333
Presurgery x Rise	2.099	5.548	111.554	.378	.706	-8.895	13.092

Note. These are fixed parameter estimates based on REML. All analyses included age, sex, and EF as main effects. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; PCT = Procalcitonin; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

Interleukin-6. As shown in

Table *17*, presurgery IL-6 (Model 1) had an almost significant main effect but no change over time. Time itself had a main effect (p = .027). There was no effect of age, sex, or EF, and the inclusion of their interaction with time did not change the pattern of results.

Rise in IL-6 (Model 2) showed a main effect and a trend toward change over time, although this was not significant. There was a main effect of time *(p* = .011). There were no effects of age, sex, or EF. The inclusion of their interaction with time negated the main effect of time but otherwise did not change the pattern of results.

Peak IL-6 (Model 3) showed a main effect and a main effect of time *(p* = .007). There was, however, no change over time, although this almost reached significance. There was no effect of age, sex, or EF, and the inclusion of their interaction with time negated the main effect of time *(p* = .184) but did not change the pattern of results.

For IL-6, there was a main effect for the presurgery, acute rise, and maximum post-surgery peak levels, yet no time interaction for any model (pre, rise, max post). A comparison of Models 4 and 5 revealed a main effect of rise and an almost significant main effect of presurgery IL-6. Time had a main effect *(p* = .009).

There was no change over time for either parameter. There were no main effects of age, sex, or EF. The inclusion of their interaction effects with time negated the main effect of time, but otherwise, the pattern of results remained the same. Model 4 had the best fit (according to the lowest AIC), as shown in

Table 17.

Table 17

Summary of main effects MMRM Analyses of IL-6 predictors of RBANS

Model	Main Effect *Sig.*	Change over Time *Sig.*	
1. Presurgery	.058	.646	
2. Rise	.021*	.079	
3. Peak	.015*	.069	
4. Combined			AIC
Presurgery			**3188.418**
Rise	.063	.653	
5. Combined with interaction term	.021*	.085	
Presurgery			3199.908
Rise	.728	.650	
Presurgery x Rise	.072		

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 4 RBANS assessments. All analyses included age, sex, and EF as main effects. Rise: Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; IL- 6= Interleukin-6; AIC = Akaike information criterion.

* $p < .05$.

As shown in Table 18, the parameter estimate for presurgery (Model 1) is not significant. For Model 2, a 100 pg/ml rise is associated with a decrease in RBANS score of 2.2 at any given time. Similarly, an increase of 100 pg/ml in peak level (Model 3) is associated with fewer points in RBANS score by 2 points. Estimates for the contribution of the presurgery level of IL-6 in Model 4 are not significant, but there is a significant

effect of rise in IL-6 such that an increase by 100 pg/ml likewise leads to 2.2 fewer RBANS points at any given time point.

Table 18

Summary of estimates of fixed parameters of MMRM analyses of IL-6 predictors of RBANS

Model	*Estimate*	*SE*	*df*	*T*	*Sig.*	*95% CI*	
						LL	*UL*
1. Presurgery	-.098	.062	107.596	-1.582	.117	-0.220	0.025
2. Rise	-.022	.011	111.853	-2.125	.036*	-0.043	-0.002
3. Peak	-.020	.010	106.184	-2.051	.043*	-0.040	-0.001
4. Combined							
Presurgery	-.097	.063	106.438	-1.542	.126	-0.221	0.028
Rise	-.022	.0106	110.539	-2.127	.036*	-0.043	-0.002
5. Combined with interaction term							
Presurgery	-.016	.095	120.427	-.172	.864	-0.205	0.172
Rise	-.019	.011	125.398	-1.73	.086	-0.041	0.003
Presurgery x Rise	-.016	.095	120.427	-.172	.864	-0.205	0.173

Note. These are fixed parameter estimates based on REML. All analyses included age, sex, and EF as main effects. Rise: Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; IL- 6= Interleukin-6; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

Interleukin-8. For IL-8, there was no main effect of either presurgery (Model 1) or its interaction with time, but a main effect of time was identified (p = .038), as seen in Table 19. There was no main effect for rise (Model 2), but there was a main effect of time (p =.012). No main effects of age, sex, or EF were found for both presurgery and rise

alone. The inclusion of their interactions with time negated the main effect of time, but otherwise, the pattern of results remained the same (data not shown). The combined model of presurgery and rise (Model 4) yielded no effect, but there was a nearly significant interaction effect of rise x time. There was also a fixed effect of time (p = .009) but no fixed effect of age, sex, or EG. Adding interaction effects with time for all parameters merely negated the fixed effect of time and interaction effect of rise with time. Model 5, which included an interaction term between presurgery and rise, showed a main effect of rise level and an interaction between presurgery and rise level (see 19). This model, however, had a worse fit according to AIC.

Table 19

Summary of fixed effects of MMRM Analyses of IL-8 predictors of RBANS

	Main Effect	Change over Time	
Model	*Sig.*	*Sig.*	
1. Presurgery	.657	.239	
2. Rise	.338	.075	
3. Peak	.006**	.043*	
4. Combined			AIC
Presurgery	.640	.186	**3174.280**
Rise	.324	.058	
5. Combined with interaction term			
Presurgery	.716	.152	3179.860
Rise	.007**	.132	
Presurgery x Rise	.003**		

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 4 RBANS assessments. These analyses include age, sex, and EF

as fixed effects. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; IL-8 = Interleukin-8; AIC = Akaike information criterion.

** p < .05. ** p < .01.*

As shown I Table 20 , the parameter estimate for peak level (Model 3) indicates that an increase in peak level by 100 pg/ml is associated with a decrease in RBANS total score at any time point of -2.7 points.

Table 20

Summary of estimates of fixed parameters from MMRM analyses of IL-8 predictors of RBANS

Model	*Esti-mate*	*SE*	*df*	*t*	*Sig.*	*95% CI*	
						LL	*UL*
1. Presurgery	-.085	.176	111.501	-.486	.628	-0.433	0.263
2. Rise	-.018	.020	134.541	-.929	.354	-0.057	0.021
3. Peak	-.027	.013	101.592	-2.118	.037*	-0.052	-0.002
4. Combined							
Presurgery	-.098	.178	109.900	-.552	.582	-0.450	0.254
Rise	-.017	.020	133.239	-.828	.409	-0.056	0.023
5. Combined with inter-action term							
Presurgery	.049	.178	111.155	.274	.784	-0.304	0.402
Rise	.195	.071	122.922	2.726	.007**	0.053	0.336
Presurgery x Rise	-.014	.004	116.903	-3.073	.003**	-0.022	-0.005

Note. These are fixed parameter estimates based on REML. These analyses include age, sex, and EF as fixed effects. Rise = Peak level post-surgery minus presurgery level; EF = Ejection Fraction; RBANS = Repeatable Battery for the Assessment of

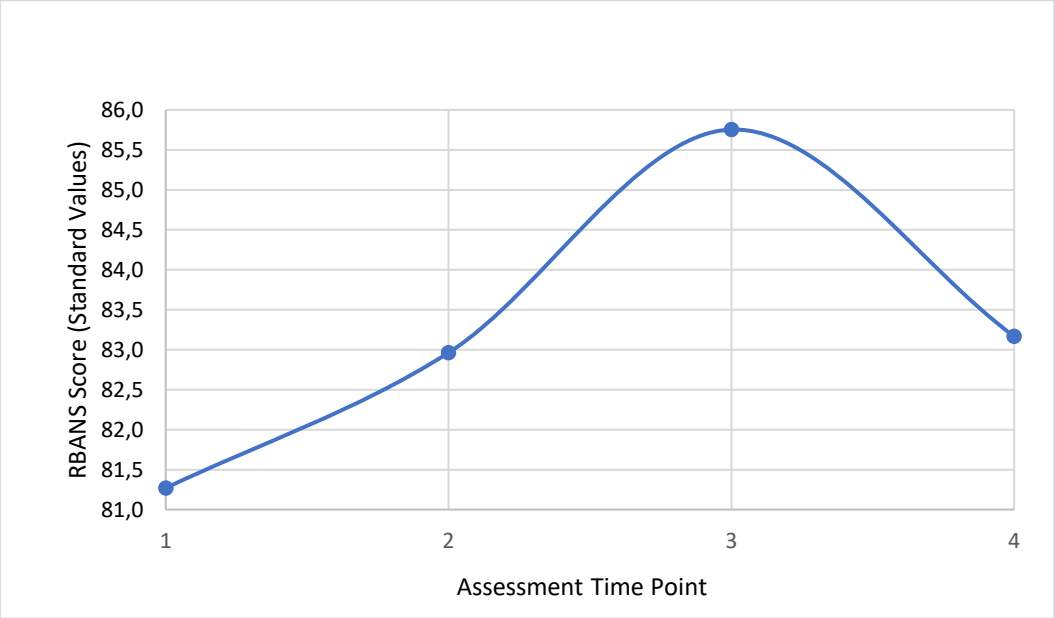
Neuropsychological Status; IL-8 = Interleukin-8; CI = confidence interval; LL = lower limit; UL = upper limit.

** p < .05. ** p < .01.*

In contrast, Model 5 parameter estimates show a better RBANS total score by almost 2 points with every 100 pg/ml increase, with a negative effect of the interaction between presurgery and rise levels of -.14 points in total RBANS score. This means chronic inflammation may negatively affect cognition, whereas the acute increase in inflammation level may be a protective factor.

Figure 6

*Interaction term peak IL-8*Time and RBANS Score*



Note. A graphical depiction of the RBANS score based on the interaction term peak IL-8*time shows a logarithmic relationship. These analyses include age, sex, and Ejection Fraction as fixed effects. Here, it becomes clear that patients' cognitive scores initially

improve. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; IL-8 = Interleukin-8.

Leukocytes. For Leukocytes, a main effect was found for time (p = .010), but no main effect of leukocytes presurgery. There was an interaction over time (Model 1), as shown in Table 21. Adding interaction terms of time with age did not change the pattern of results. Rise (Model 2) and Peak Leukocytes (Model 3) yielded no significant main effect and no interaction with time.

The combined models show similar patterns, with Model 4 (no interaction term between presurgery and rise) having the best fit, according to AIC. There is no main effect of either presurgery or rise levels in this model, but a significant change over time for the presurgery level. In contrast, in Model 5, with a similar level of fit, presurgery Leukocyte level was a significant predictor of RBANS score, and here, too, there was an interaction with time.

Table 21

Summary of fixed effects of MMRM Analyses of Leukocytes predictors of RBANS

	Main Effect	Change over Time	
Model	*Sig.*	*Sig.*	
1. Presurgery	.165	.032*	
2. Rise	.644	.073	
3. Peak	.189	.061	
4. Combined			AIC
Presurgery	.154	.040*	**3111.290**
Rise	.568	.091	
5. Combined with interaction term			
Presurgery	.043*	.039*	3132.908
Rise	.243	.092	
Presurgery x Rise	.240		

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 4 RBANS assessments. These analyses include age, sex, and Ejection Fraction as fixed effects. Rise: Peak level post-surgery minus presurgery level; EF = Ejection Fraction, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; AIC = Akaike information criterion.

** $p < .05$.*

As seen in Table 22, there were no significant parameter estimates for the fixed effects of any of the models.

Table 22

Summary of estimates of fixed parameters of MMRM Analyses of Leukocyte Count predictors of RBANS

Model	*Estimate*	*SE*	*df*	*t*	*Sig.*	*95% CI*	
						LL	*UL*
1. Presurgery	-.476916	.70	115.233	-.678	.499	-1.870	.916
2. Rise	.007211	.01	103.736	.462	.645	-.023	.038
3. Peak	.009	.01	102.518	1.051	.296	-.008	.026
4. Combined							
Presurgery	-.633	.69	115.758	-.915	.362	-2.00	.736
Rise	-.008	0.02	106.046	.529	.598	-.022	.039
5. Combined with inter-action term							
Presurgery	-1.210	.84	125.049	-1.432	.155	-2.88	.462
Rise	-1.378	1.17	122.035	-1.174	.243	-3.70	.945
Presurgery x Rise	.156	.13	122.019	1.181	.240	-.105	.418

Note. These are fixed parameter estimates based on REML. These analyses include age, sex, and Ejection Fraction as fixed effects. Rise: Peak level post-surgery minus presurgery level; EF = Ejection Fraction, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CI = confidence interval; LL = lower limit; UL = upper limit.

For Models 4 and 5, despite the lack of significance of the estimated parameters, it should be noted that the presurgery and rise levels are all negative, indicating a negative association.

Discussion

Pathology Levels. An important issue regarding comparing chronic and acute systemic inflammation was whether and to what extent pathological inflammation levels were found in the presurgery versus post-surgery period. The answer depends on the particular biomarker used. CRP and IL-6 were pathological in more than 60% of patients before surgery; IL-8 was pathological in about one-third of patients. The other markers, PCT and leukocytes, were largely unremarkable before surgery. During the post-surgery period, there was a major shift, with CRP and IL-6 shifting upward of 97% of the patient cohort and IL-8 moving to 74% pathology. Likewise, PCT moved from a handful of pathological patients using only the lowest threshold to almost 30% pathological in the post-surgery period, cumulatively using any given threshold. Leukocytes, however, did not reach a pathological maximum level post-surgery for any patient; the handful who had had pathological levels before surgery returned to normal.

Differences in biomarkers across SIRS diagnostic groups. Altogether one-third of the patients in this study had a diagnosis of SIRS during the post-surgery period. An

examination of the dependency of the absolute levels of cytokines and leukocyte count upon the diagnosis of SIRS yielded only a few differences: the rise in levels of PCT from baseline to maximum post-surgery, as well as in the peak level of PCT post-surgery itself, and leukocyte at baseline differed across groups, with higher levels among SIRS patients. No serum biomarkers differed based on SIRS classification. Hence, further examining associations of pro-inflammatory serum biomarker levels with cognition was warranted.

Hypothesis 1: Correlation among chronic and acute levels of serum biomarkers. A twofold comparison was conducted concerning the first question about whether higher levels of chronic inflammation are associated with indicators of acute inflammation. First, low to medium strength correlations between presurgery and peak levels were confirmed, with IL-6, CRP, and PCT having the lowest strengths of the association at approximately $r = .30$ and IL-8 and LZ having the highest just above $r = .50$. In contrast, the strength and direction of association between presurgery and rise in levels were very small, and depending on the biomarker, the correlations could either be positive (IL-6, IL-8) or negative (CRP, PCT, LZ). Hence, examining presurgery and rise levels as individual predictors of cognitive performance was warranted.

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance over time. Based on simple correlation, there are only weak and mostly non-significant correlations between cognitive performance at any given time point and any given proinflammatory serum biomarker or SIRS diagnosis. A relatively weak negative correlation was leukocyte count and MMSE score at the presurgery assessment. At the 3-month RBANS assessment, there was a weak negative association between RBANS score and peak values of CRP and PCT, although no meaningful associations were found for the day three or the 12-month RBANS assessment. Due to the nature of this dataset, there is an important caveat: This type of simple analysis is

vulnerable to bias due to the truncation of the dataset in the SIRS group. Additionally, predictive power is lost due to the dataset's longitudinal nature and the cognitive assessments' high intercorrelation. Hence, a Multilevel Repeated Measures Model was more pertinent to answering this question, to which we turn next.

MMRM analysis revealed a main adverse effect of SIRS diagnosis on cognitive performance. In other words, those with a SIRS diagnosis attained on average six fewer RBANS points at any given time. The cognitive trajectory remained the same across diagnoses, so this effect does not accelerate cognitive impairment compared to those without a SIRS diagnosis.

For CRP, presurgery and rise levels were strongly negatively associated with cognitive performance. Presurgery CRP lowered cognitive performance by 12 RBANS points at any given time for a 100 unit increase. The post-surgery rise level was also associated with a further 6.6 point fewer points in performance in the same model, although there was no interaction between these regressors.

PCT rise or peak alone were negatively associated with cognition in simple models, and PCT_{rise} almost reached significance when controlling for presurgery level – with an estimated effect of approximately 12 fewer points in RBANS score at any given time for a 10 unit rise.

IL-6 simple models and presurgery and rise levels in a combined model were negatively associated with cognitive performance, although the fewer points were much smaller than SIRS, CRP, or PCT, around 2 points for rise level and around 1 point for presurgery level. The combined model showed that the rise level, rather than the presurgery level, is negatively associated with cognitive performance.

The pattern for IL-8 was different, and the effects were comparatively small. There was a negative effect of the interaction between presurgery and rise levels and cognition

of fewer than 2 points for every 100-unit rise. There was, oddly, a positive effect of rise level on cognition and an almost significant effect of change over time.

For Leukocytes, the presurgery level in the combined model with interaction term was negatively associated with cognitive performance, with a significant change over time. The effects on cognition appeared to be very small, and the parameter estimates did not reach significance.

Hypothesis 3: Do chronic and acute systemic inflammation negatively impact the trajectory of cognitive performance over time. The question of change over time was evaluated in both simple models of presurgery, rise and peak levels, and combined models of presurgery and rise, including interaction terms. These analyses showed a significant change over time in IL-8 peak level postsurgery, with a greater decline in cognition. The opposite was true for LZ presurgery, with a greater increase in cognition over time. Otherwise, no significant changes were identified over time for SIRS or CRP, PCT, or IL-6.

Hypothesis 4: Is there an interaction between chronic and acute inflammation on cognitive performance. When interaction terms between presurgery and rise levels were added to the MMRM models of fixed effects, there was no interaction between these levels for CRP, PCT, IL-6, or Leukocytes. Despite this, for PCT, the inclusion of this interaction term had a slightly better model fit. In contrast to all other biomarkers, there was an interaction between presurgery and rise levels of IL-8, with a small but negative association with cognition.

Study 2. General Cardiac Surgery Patients

The original research question for this second study was to identify factors that predispose patients to postoperative delirium after cardiac surgery, including intraoperative procedures, medication, and intensive care unit procedures and therapies (Guenther et al., 2013). Long-term chronic inflammation was not necessarily part of the presurgery medical history for this collective. The operations required here were for mitral valve or aortic valve insufficiency or regurgitation due to various structural abnormalities, stenosis, or both. Inflammation-associated plaque build-up, as in the TAVI patients, was relevant only in some patients, although a chronic inflammatory process could be expected in some portion of these patients prior to surgery. Whether presurgery and post-surgery levels of inflammation and SIRS were negatively associated in this different and more diverse population could validate the first study's findings.

Hypotheses. The same questions were posed in this study as in the preceding study.

1) Hypothesis 1: Are higher chronic inflammation levels associated with acute inflammation indicators?
2) Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance at any time point?
3) Hypothesis 3: Do chronic and acute systemic inflammation influence the *trajectory* of cognitive performance over time?
4) Hypothesis 4: Is there an *interaction* between chronic and acute inflammation on cognitive performance?

Specifically, inflammation in Study 2 was operationalized in a much more restricted manner (CRP, LZ, and SIRS Diagnosis) and compared to a cognitive screen (MMSE) in the main cohort. A subset of patients (around 1/3) received more thorough cognitive

testing based on RBANS (RBANS Subgroup). Hence, a thorough examination of the RBANS Subgroup data was conducted similarly to Study 1.

Methods

Recruitment. All patients scheduled for major surgery (n = 401) during 2014-2016 through December 2009 were consecutively screened at the Department of Cardiology at the University Hospital Bonn for inclusion in this study. A total of 215 heterogeneous patients were identified for inclusion in the study. They were scheduled for a planned cardiac operation due to coronary heart disease or heart valve failure. Inclusion criteria were: Over age 49, German-speaking, scheduled elective heart surgery. Exclusion criteria were: non-German speaking patients, participation in another study, less than 50 years of age, and unscheduled surgeries.

Ethical Considerations.

This study protocol was positively evaluated by the Medical Ethics Review Board of the University Hospital Bonn (IRB Number 058/09) "Predictors of postoperative cognitive performance level and activities of daily living in cardiac surgery patients" (original German language title: "Prädiktoren des postoperativen kognitiven Leistungsniveau und Aktivitäten des täglichen Lebens bei kardiochirurgischen Patienten"). This specific analysis was separately positively reviewed by the chair of the Medical Ethics Review Board of the University Hospital Bonn since needed clinical parameters and biomarker information was not included in the original protocol and had to be assessed from electronic patient files (IRB Number 133/13).

The study was conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for Good Clinical Practice and the relevant national regulations and the Declaration of Helsinki, as laid out in the Directive 2001/20/EC of the European

Parliament and of the Council of 4 April 2001 ("Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the Approximation of the Laws, Regulations and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use," 2002).

The study was sponsored by the University of Bonn Medical Center and conducted under Dr. Ulf Günther, Managing Senior Physician at the University of Bonn Medical Center.

Surgery Types. Surgery included "closed surgery," i.e., *coronary artery bypass graft (CABG),* which inserts a shunt around narrowed and blocked coronary arteries to boost blood flow to the heart muscle. This procedure does not require opening the chest since it can be conducted with minimal invasion. Further, "open surgery" patients were recruited who had an *aortic valve or mitral valve replacement,* in which the valves are removed and replaced with an artificial valve, requiring a large incision in the chest. A further type of open-heart surgery (O-H S) was *thoracic aneurysm repair,* which corrects over-enlargement of the aorta in the area of the thorax or chest. Here a stent-graft is inserted into the aorta, around which the aneurysm eventually shrinks. The details of the surgical procedures have been published previously (Guenther et al., 2013).

Cognitive Assessment. The *Mini-Mental Status Examination (*Folstein, 1975) was conducted at the clinic prior to surgery, which consisted of 30 points as described in the Overview Section describing common methods across studies. In addition, a *telephone variant of the MMSE* with a total of 22 points was conducted six months after surgery. The telephone version of the MMSE excluded the following items from the original MMSE because they required visual stimuli or manual manipulation: naming objects, comprehension/praxis, reading and writing a sentence, and drawing/figure copy.

Subset Cognitive Assessment. A subset of patients (n = 35) underwent extensive cognitive testing presurgery at six months post-surgery using the *Repeatable Battery for the Assessment of Neuropsychological Status* (RBANS; Randolph et al., 1998).

Proinflammatory Serum Biomarkers. Blood samples were drawn before cardiac surgery as part of the presurgical work-up and as medically indicated at several points in the post-surgery period. Leukocytes (gL) and C-Reactive Protein (mg/L) included pro-inflammatory biomarkers. The presurgical and maximum value of Leukocytes and CRP in the postsurgery period was used for comparison purposes. The differential between presurgery and maximum postsurgery indicated the acute inflammatory increase due to surgery and designated "rise," as in Study 1.

Demography, Comorbidities, Perioperative Parameters. Age, sex, body-mass index, mortality, atrial septal defect, chronic atrial fibrillation, chronic pulmonary disease, heart insufficiency, heart infarct, and ejection fraction were assessed. Clinical parameters included type of surgery, length of surgery, mortality, SIRS Diagnosis, neurological complications, ventilator days, delirium days, Glasgow coma scale (GCS), which was averaged for the time during ICU stay, Geriatric Depressions Scale, length of stay at the hospital and the intensive care unit and thrombocytes ($10*3/mm^3$). Lastly, the ejection fraction (EF), a measure of heart insufficiency, was also included as a fixed effect in cognitive data analysis.

Statistics and data analysis.

Missing data Analysis. Missing value analysis was conducted using SPSS 22.0, as recommended in Tabachnik and Fidell (2007), including estimation of means and t-tests and evaluations of the pattern of missing data. The specific SPSS Output of these analyses is included in Appendix C. In total, 38 participants (16.8%) who were assessed at baseline (wave one n = 224) were not present for the second assessment wave (wave

two n = 188). Further, an analysis of missing serum biomarker data revealed that 18 participants (8% of the baseline sample) had no blood sample taken. An estimation of means analysis indicated that Little's MCAR test was not significant: ($\chi^2_{(df:11)}$ = 12.143, p = .353; see Appendix C). Hence, data were considered missing completely at random.

Bivariate Pearson correlation of cognition and biomarker data, chi-square tests of frequency and ordinal data, and independent sample 2-sided student T-Tests were conducted for continuous descriptive data.

Hierarchical multiple regression analysis was applied to identify what parameter contributed to the variance of the MMSE pre-operatively or post-operatively using presurgery, rise level, and maximum level of a given cytokine or SIRS diagnosis with age as an additional regressor.

Subset analysis using Multilevel Modelling with Repeated Measures (MMRM). In parallel to Study 1, but only for a subgroup of patients who had been comprehensively assessed, a sequence of models was then analyzed using both the presurgery biomarker and rise level, and, in the next step, interaction term to identify the effects of the presurgery and rise levels when both are included in the same model and find best model fit.

Using MMRM, change in cognitive performance between the presurgery and follow-up assessment could be analyzed in this subgroup since parallel and reasonably reliable versions of the RBANS battery were used (*Cronbach's alpha* = .83) at both time points (McKay et al., 2007).

Results

Descriptive Characteristics. There were several differences between those with and without SIRS diagnosis summarized in Table 23 and Table 24. Leukocyte levels before surgery were much lower, at around 7%, growing to almost 90% post-surgery. There

were no differences in pathology according to SIRS diagnosis. There were no differences in the frequency of surgery either for the entire group of patient subjects or the subgroups. Thus, those diagnosed with SIRS had considerably longer hospital, and ICU stays, higher Glasgow coma scores (indicative of more brain injury), and a longer duration of delirium and ventilator days. There was no difference in the frequency of neurological complications during surgery. There were no differences in pre- or postsurgery MMSE performance according to SIRS diagnosis. Thrombocyte (platelet) count was well within the normal range for SIRS and nonSIRS subgroups as well as for the whole sample.

Regarding differences in levels of inflammatory cytokines as continuous variables, the SIRS group presented with considerably higher peaks post-surgery, rise levels of CRP, and rise levels of leukocytes compared to the non-SIRS group. Regarding pathological scores, around half of the whole group had pathological CRP prior to surgery, in contrast to the 100% pathological peak levels postsurgery for CRP.

Table 23

Means and standard errors for continuous patient and clinical characteristics

	Total Group			No SIRS			SIRS							95% CI for Difference		
Parameter	*N*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*LL*	*UL*	*Sig.*
Age (years)	218	70.02	0.68	180	69.53	0.78	38	72.34	1.30	-1.561	216.00	-2.81	1.80	-6.37	0.74	.120
LOS Hospital (days)	216	18.55	0.99	178	16.07	0.79	38	30.18	3.70	-3.726	40.48	-14.12	3.78	-21.77	-6.46	.001**
LOS ICU (days)	216	4.69	0.53	178	3.00	0.34	38	12.58	2.17	-4.346	38.84	-9.58	2.20	-14.04	-5.12	<.001***
BMI	212	27.22	0.28	174	27.18	0.31	38	27.44	0.71	-0.35	210.00	-0.26	0.75	-1.74	1.22	.727
Ventilator (days)	214	2.63	0.34	176	1.63	0.24	38	7.23	1.35	-4.061	39.35	-5.60	1.37	-8.38	-2.81	<.001***
Avg. GCS	214	4.75	0.21	176	4.15	0.19	38	7.51	0.71	-4.512	42.31	-3.36	0.74	-4.86	-1.86	<.001***
Delirium (days)	212	0.74	0.09	176	0.58	0.09	36	1.53	0.24	-3.585	45.70	-0.95	0.26	-1.48	-0.42	.001**
Surgery (Minutes)	141	250.96	6.91	117	252.69	7.55	24	242.50	17.50	0.535	32.14	10.19	19.06	-28.62	49.01	.596
Thromboscytes (10*3/mm³)	218	239.81	4.65	180	240.83	4.95	38	235.00	12.86	0.474	216.00	5.83	12.28	-18.39	30.05	.636
GDS	216	1.98	0.12	178	1.94	0.13	38	2.18	0.27	-0.759	214.00	-0.25	0.32	-0.89	0.39	.449
MMSE pre-op	218	27.00	0.20	180	27.02	0.22	38	26.92	0.47	0.19	216.00	0.10	0.53	-0.95	1.15	.850
Tel. MMSE post-op	183	18.93	0.22	154	18.95	0.22	239	18.83	0.74	0.163	33.20	0.13	0.78	-1.46	1.72	.872
LZ pre-op (G/L)	218	7.28	0.21	180	7.22	0.24	38	7.55	0.39	-0.589	216.00	-0.33	0.55	-1.42	0.77	.556
post-op (G/L)	217	15.31	0.40	179	15.12	0.43	38	16.22	1.00	-1.041	215.00	-1.09	1.05	-3.17	0.98	.299
rise (G/L)	218	7.96	0.29	180	7.47	0.30	38	10.29	0.77	-3.76	216.00	-2.82	0.74	-4.29	-1.34	<.001***
CRP pre-op (mg/L)	218	6.46	0.76	180	5.81	0.82	38	9.52	1.99	-1.72	50.26	-3.71	2.15	-8.04	0.62	.092
post-op (mg/L)	218	133.77	4.39	180	138.44	4.70	38	111.69	11.22	2.336	216.00	26.75	11.45	4.18	49.32	.020*
rise (mg/L)	218	127.31	4.28	180	132.62	4.59	38	102.16	10.58	2.739	216.00	30.46	11.12	8.54	52.38	.007**

Note. Independent Samples Test, 2-sided significance, equal variances assumed, alpha-level = .05. SIRS = Systemic Inflammatory Response Syndrome; LOS = Length of Stay; BMI = Body Mass Index; Avg. GCS = Average Glasgow Coma Score; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination (max. 30 Points); Tel. MMSE = Telephone variant of MMSE (max 22 Points); LZ = Leukocyte Count; CRP = C-reactive Protein.

* $p < .05$. ** $p < .01$. *** $p < .001$.

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Leukocyte levels before surgery were much lower, at around 7%, growing to almost 90% post-surgery. There were no differences in pathology according to SIRS diagnosis. There were no differences in the frequency of surgery either for the entire group of patient subjects or the subgroups (see Table 24).

Table 24

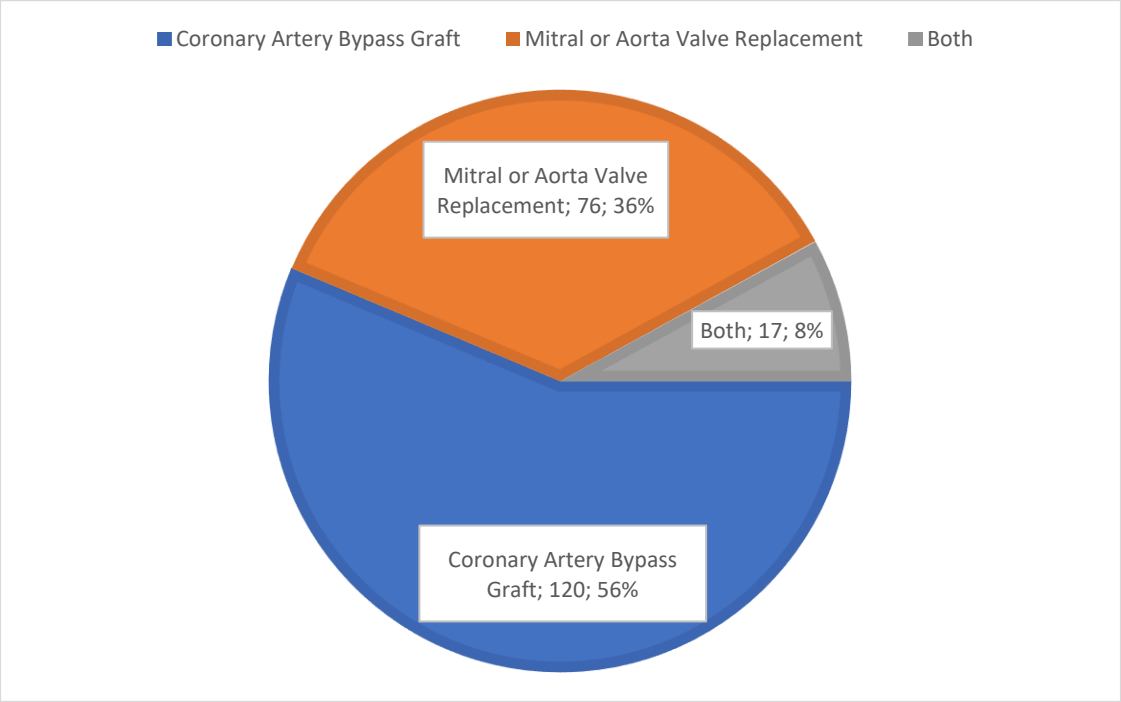
Sample sizes, frequencies, and percent of noncontinuous patient & clinical characteristics

	Total			No SIRS			SIRS					
Parameter	*N*	*Freq.*	*%*	*n*	*Freq.*	*%*	*n*	*Freq.*	*%*	*df*	χ^2	*Sig.*
Sex (male)	217	144	66.1%	179	119	66.1%	38	25	65.8%	1	.007	.935
Mortality	213	9	4.1%	175	6	3.3%	38	3	7.9%	1	.215	.203
O-H S	214	97	44.5%	176	75	41.7%	38	22	57.9%	1	2.945	.086
C-H S	214	117	53.7%	176	101	56.1%	38	16	42.1%	1	2.945	.086
O-H MS	214	24	11.0%	176	20	11.1%	38	4	10.5%	1	.022	.882
CABG	215	137	62.8%	177	117	98.3%	38	20	52.6%	1	2.455	.117
Valve Implant	214	93	42.7%	176	72	40.0%	38	21	55.3%	1	2.621	.105
Atrial Septal Defect	214	1	0.5%	176	1	0.6%	38	0	0.0%	1	.217	.641
Aortic Aneurysm Repair	214	8	3.7%	176	7	3.9%	37	1	0.5%	1	.157	.692
Chronic Atrial Fibrillation	215	32	14.7%	177	23	12.8%	38	9	23.7%	1	2.822	.093
Chronic Pulmonary Disease	216	25	11.5%	178	20	11.1%	38	5	13.2%	1	.113	.737
Heart Insufficiency	216	158	99.1%	178	129	71.7%	38	29	76.3%	1	.238	.627
Heart Infarct	216	57	26.1%	178	47	26.1%	38	10	26.3%	1	.000	.991
Neurological Complications	208	10	4.6%	174	6	3.3%	34	4	10.5%	1	3.704	.054

Note. Pearson chi-square test of homogeneity (two-sided asymptotic) for categorical data between No SIRS and SIRS, asymptotic significance testing; cases were excluded test-by-test for missing data. SIRS = Systemic Inflammatory Response Syndrome; O-H S = Open-heart surgery; C-H S = Closed-heart surgery; O-H MS = Open-heart multiple surgeries; CABG = Coronary Artery Bypass Graft.

Figure 7

Surgery type with frequencies and percentages for the total sample



As shown in Figure 7, two types of surgery were conducted, which did not differ by SIRS status using Pearson two-sided chi-square testing ($\chi 2$ (2, 218) = 3.117, p = .210). The average number of days of CRP determination prior to surgery was *M (SD)* 4.00 (3.66) days, and after surgery was on average 4.95 (5.11) days later. The leukocyte determination prior to surgery was 3.61 (3.47) days before and 1.49 (3.23) days after surgery.

As depicted in Table 25, there was a significant shift in the number of pathological inflammatory biomarker values prior to and after surgery. The number of pathological CRP values prior to surgery was less than half, and the number of pathological CRP values post-surgery was more than 90 percent of the cohort. The number of patients with pathological leukocyte counts (either too high or too low) was less than 10 percent prior to surgery but over 95% post-surgery.

Table 25

Descriptive statistics pathological status at baseline and peak of inflammatory biomarkers

	Baseline			Peak		
Inflamm. Biomarker	Normal *Freq. (%)*	Pathol. *Freq. (%)*	Missing *Freq. (%)*	Normal *Freq. (%)*	Pathol. *Freq. (%)*	Missing *Freq. (%)*
CRP	98 (53.5%)	98 (43.4%)	7 (3.1%)	0 (0%)	211 (93.4%)	15 (6.6%)
LZ	208 (92%)	16 (7.1%)	2 (.9%)	27 (11.9%)	196 (96.7%)	3 (1.3%)

Note. Cut-scores for LZ was age-based. The LZ had lower and upper cut-points, accounted for in the calculation. Reference ranges and clinical designations derived from the internal documents for each biomarker at University Hospital Bonn Central Laboratory's intranet website: http://www.meb.uni-bonn.de/klinbiochem/laborbuch November 27, 2016. CRP = C-reactive Protein, LZ = Leukocyte Count.

Correlational Analysis. Correlation analysis, means, and standard deviations are reported in Table 26 below. Table 27 indicates expected negative correlations between MMSE assessments and age and delirium, a known risk factor for cognitive impairment postsurgery. Small associations between CRP peak and CRP rise with MMSE tests were identified. Leukocyte levels had no association with MMSE. Kendall's Tau bivariate correlation analysis yielded no association between presurgery and peak levels of either CRP or Leukocytes. Presurgery CRP and Leukocyte levels did correlate, but the postoperative rise levels did not. Likewise, SIRS diagnosis was not associated with MMSE scores.

Regarding surgery type, open-heart surgery correlated negatively with presurgery MMSE but not with postsurgery performance. In contrast, closed-heart surgery positively associated with presurgery MMSE and had no association with post-surgery cognition. Open-heart multiple surgeries did not correlate with either cognitive outcome.

Table 26

Means, standard deviations or frequencies and intercorrelations MMSE, clinical and biomarkers of inflammation

			Zero-Order *r*								
Parameters	*M*	*SD*	LZ peak (gL)	LZ pre-op (gL)	CRP rise (mg/L)	CRP peak (mg/L)	CRP pre-op (mg/L)	SIRS	Age (years)	Tel. MMSE post-op	MMSE pre-op
Tel. MMSE pre-op	26.96	2.901									.480**
Age (years)	69.73	9.221								-.176**	-.181**
SIRS (n, %)	29	16%							.095	.001	-.014
CRP pre-op (mg/L)	6.32	11.382						.115*	.008	-.083	-.073
peak (mg/L)	135.48	65.425					.161**	-.162**	.000	-.114*	-.062
rise (mg/L)	129.15	64.560				.922**	.079	-.175**	-.003	-.108*	-.058
LZ pre-op(gL)	7.23	3.274			.009	.026	.201**	.050	-.102*	.069	.021
peak (gL)	15.29	5.879		.055	.023	.031	.025	.034	-.001	-.041	-.037
rise (gL)	7.87	4.268	.218**	.062	-.049	-.050	.033	.196**	-.064	.031	.035

Note. Kendall's Tau Correlation. Listwise deletion of cases, *n* = 182. MMSE = Mini-Mental State Examination (max. 30 Points); Tel. MMSE = telephone variant of MMSE (max. 22 Points); SIRS = Systemic Inflammatory Response; CRP = C-Reactive Protein; LZ = Leukocyte Count; pre-op = preoperative, post-op = postoperative; peak = highest level after operation; rise = difference between preoperative and peak level.

** $p < .05$. ** $p < .01$*

Table 27

Correlation analysis (2-tailed) of cognitive, biomarker, as well as clinical parameters

Variables	MMSE pre-op	Tel. MMSE post-op	Age	BMI	Ventil. Days	GCS	Delirium Days	O-H S.	C-H S
MMSE pre-op	-								
Tel. MMSE pos-op	.480**	-							
Age	-.181**	-.176**	-						
BMI	-.007	-.057	-.139**	-					
Ventilator (days)	-.043	-.021	.068	.040	-				
Avg. GCS	-.062	-.007	.126*	-.016	.412**	-			
Delirium (days)	-.165**	-.153*	.212**	-.047	.365**	.471**	-		
CRP pre-op	-.073	-.083	.008	.042	.107*	.036	.074		
Peak	-.062	-.114*	.000	.074	-.139**	-.280**	-.176**		
Rise	-.058	-.108*	-.003	.075	-.154**	-.295**	-.180**		
LZ pre-op	.021	.069	-.102*	.062	.097*	.031	.024		
Peak	-.037	-.041	-.001	.044	.017	.020	.040		
Rise	.035	.031	-.064	.140**	.135**	.056	.085		
SIRS	-.014	.001	.095	.029	.398**	.320**	.314**	-	
O-H S	-.129*	.007	.128*	-.169**	.121*	.085	.165*	.117	
C-H S	.129*	-.007	-.128*	.169**	-.121*	-.085	-.165*	-.117	
O-H MS	.014	.133*	.032	-.062	.040	.046	.049	-.010	.390**

Note. Kendall's Tau (2-sided), pairwise case deletion in case of missing, *n* = 182. MMSE = Mini-Mental State Examination; Tel. MMSE = telephone variant of MMSE; BMI = Body Mass Index; GCS = Glasgow Coma Score; SIRS = Systemic Inflammatory Response; CRP = C-

Reactive Protein; LZ = Leukocyte Count; pre-op = preoperative, post-op = postoperative; peak = highest level after operation; rise = difference between preoperative and peak level; O-H S = Open-heart surgery; C-H S = Closed-heart surgery; O-H MS = Open-heart multiple surgeries.

** $p < .05$. ** $p < .01$.*

General Linear Modelling (GLM) and multiple linear regression models were carried out using age, baseline levels and rise levels of Leukocytes and C-Reactive Protein, and SIRS/Sepsis diagnosis as predictors of pre-operative MMSE as the dependent variable.

Diagnosis of SIRS. A hierarchical multiple regression using age and SIRS as regressors are summarized in Table 28, which shows the unstandardized regression coefficients (*B*), the standardized regression coefficients (β), the standard error of as well as the lower and upper limits of the 95% confidence interval of the unstandardized coefficients. This analysis resulted in a single predictor model which only included age and an explained variance of 4.1% ($p = .004$).

Table 28

Hierarchical regression results for SIRS and MMSE Score

	Coefficients					95% CI of *B*		*Model Change Statistics*		
Variable	*B*	*β*	*SE*	*T*	*Sig.*	*LL*	*UL*	Δ *R2*	*Adj. R2*	*Sig.*
Age (years)	-.222	-.065	.020	-3.339	.001**	-0.104	-0.027	.049	.045	.001**
SIRS	.011	.084	.524	.160	.873	-0.950	1.117	.000	.041	.873

Note. Intercept = 31.589. SIRS = Systemic Inflammatory Response Syndrome, MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .01$.

A second analysis using stepwise linear regression yielded a similar result, with only age included in the model ($B = .222$, adj. $R^2 = .045$, $p = .001$). SIRS was excluded from the model. These analyses show that SIRS had no main effect on pre-operative MMSE score.

CRP. Hierarchical multiple regression models as summarized in Table 29 using age as a predictor and, separately, presurgery CRP, postsurgery CRP peak, and CRP rise levels yielded no model in which CRP level was a significant predictor for pre-operative MMSE performance. When age was excluded from the model, no models achieved significance. In addition, hierarchical regression using the same combinations of variables yielded only age as a relevant predictor. Changing the order of the CRP level entered into the model did not essentially change the results.

Table 29

Hierarchical regression results for CRP and pre-operative MMSE

	Coefficients					95% CI of *B*		Model Change Statistics		
Variable	*B*	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:										
Age (years)	-.065	-.065	.020	-3.334	.001**	-0.104	-0.027	.049	.045	.001**
CRP presurgery	-.005	-.005	.018	-.257	.797	-0.039	0.030	.000	.041	.797
Model 2:										
Age (years)	-.217	-.064	.020	-3.279	.001**	-0.102	-0.026	.049	.045	.001**
CRP peak	-.090	-.004	.003	-1.364	.174	-0.010	0.002	.008	.049	.174
Model 3:										
Age (years)	-.218	-.064	.020	-3.284	.001**	-0.103	-0.026	.049	.045	.001**
CRP rise	-.090	-.004	.003	-1.352	.178	-0.010	.0002	.008	.049	.178
Model 4:										
Age (years)	-.217	-.064	.020	-3.272	.001**	-0.103	-.025	.045	.041	.001**
CRP presurgery	-.012	-.003	.018	-o.188	.851	-0.038	0.031	.041	.044	.797
rise	-.089	-.004	.003	-1.337	.183	-0.010	0.002	.044	.041	.183
Model 5:										
Age (years)	-.219	-.064	.019	-3.306	.001**	-0.103	-0.026	.049	.045	.001**
CRP presurgery	-.179	-.047	.034	-1.403	.162	-0.114	0.019	.000	.041	.797
Rise	-.148	-.007	.004	-1.929	.055	-0.014	0.000	.008	.044	.183
presurgery x rise	.206	.000	.000	1.527	.128	0.000	0.001	.010	.050	.128

Note. CRP = C-reactive Protein, MMSE = Mini-Mental State Examination; peak = highest level after operation; rise = difference between preoperative and peak level; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .01$.

Leukocytes. Hierarchical multiple regression models, as summarized in Table 30, using age as a predictor and, separately, presurgery Leukocyte level, postsurgery

Leukocyte peak, and Leukocyte rise levels yielded no model in which Leukocyte level was a significant predictor for pre-operative MMSE performance.

Table 30

Hierarchical regression results for Leukocytes and pre-operative MMSE

	Coefficients					95% CI of *B*		Model Change Statistics		
Variables	*B*	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:			.020		.001*					.001*
Age (years)	-.220	-.065		-3.316	*	-0.01	-0.03	.049	.045	*
LZ presurgery	.050	.048	.064	.755	.451	-0.01	0.17	.003	.043	.451
Model 2:			.020		.001*					.001*
Age (years)	-.221	-.065		-3.314	*	-0.10	-0.03	.048	.044	*
LZ peak	-.033	-.017	.034	-.499	.618	-0.08	0.05	.001	.041	.618
Model 3:			.020		.001*					.001*
Age (years)	-.224	-.066		-3.322	*	-0.11	-0.03	.049	.045	*
LZ rise	-.012	-.008	.047	-.175	.861	-0.10	0.08	.000	.041	.861
Model 4:			.020		.001*					.001*
Age (years)	-.224	-.066		-3.323	*	-0.11	-0.03	.049	.045	*
LZ presurgery	.056	.054	.066	.817	.415	-0.08	0.18	.003	.043	.451
Rise	-.025	-.017	.048	-.359	.720	-0.11	0.07	.001	.039	.720
Model 5:			.020							.001*
Age (years)	-.222	-.065		-3.199	.002*	-0.11	-0.03	.049	.045	*
LZ presurgery	.085	.081	.163	.498	.619	-0.24	0.40	.003	.043	.451
Rise	-.005	-.003	.088	-.039	.969	-0.18	0.17	.001	.039	.720
peak x rise	-.040	-.002	.009	-.185	.854	-0.02	0.02	.000	.035	.854

Note. LZ = Leukocyte Count; MMSE = Mini-Mental State Examination; peak = highest level after operation; rise = difference between preoperative and peak level; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$. ** $p < .01$.*

As with CRP, no models achieved significance when age was excluded from the model. Stepwise regression using the same variables did not change results, yielding only age as a predictor of pre-operative MMSE score.

Post-operative MMSE.

Diagnosis of SIRS. A hierarchical multiple regression using pre-operative MMSE, age, and SIRS as regressors is summarized in Table 31. Including pre-operative MMSE was meant to determine group differences in cognition while controlling for pre-operative cognitive ability. Neither age nor SIRS diagnosis was a significant predictor in this model. These were highly colinear (VIF of 1.042 and 1.002, respectively). A stepwise regression analysis resulted in a single predictor model based on age, with an explained variance of 4.06% ($p < .001$).

Table 31

Hierarchical regression results for SIRS and postoperative MMSE

	Coefficients					95% CI of *B*		*Model Change Statistics*		
Variable	*B*	*B*	*SE*	*T*	*Sig.*	*LL*	*UL*	Δ *R2*	*Adj. R2*	*Sig.*
Pre-operative MMSE	.637	.673	.062	10.832	<.001***	0.55	0.80	.406	.403	<.001***
Age (years)	-.004	-.001	.017	-0.070	.944	-0.03	0.03	.000	.399	.961
SIRS	.014	.113	.474	0.239	.812	-0.82	1.05	.000	.396	.812

Note. MMSE = Mini-Mental State Examination; SIRS = Systemic Inflammatory Response Syndrome; pre-op = preoperative; CI = confidence interval; LL = lower limit; UL = upper limit.

*** $p < .001$.

A second analysis using stepwise linear regression yielded a similar result, with only pre-operative MMSE included in the model (B = .637, adj. R^2 = .403, p < .001). SIRS and age were excluded from the model. These analyses show that SIRS had no main effect on post-operative telephone MMSE score.

CRP. Hierarchical multiple regression models as summarized in Table 32using age as a predictor and, separately, presurgery CRP, postsurgery CRP peak, and CRP rise levels yielded no model in which CRP level was a significant predictor for post-operative MMSE performance. When age was excluded from the model, no models achieved significance. In addition, stepwise regression using the same combinations of variables yielded only age as a relevant predictor. Changing the order of the CRP level entered into the model did not essentially change the results.

Table 32

Hierarchical regression model summaries for CRP for post-surgery MMSE

	Coefficients					95% CI of *B*		Model Change Statistics		
Variable	*B*	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1: Presurgery										
MMSE	.640	.675	.062	10.871	<.001***	0.64	10.87	.406	.403	<.001***
Age (years)	-.003	-.001	.017	-0.058	.953	-0.00	-0.06	.000	.399	.961
CRP presur-gery	.043	.011	.015	0.750	.454	0.04	0.75	.002	.398	.454
Model 2: Presurgery										
MMSE	.631	.666	.063	10.600	<.001***	0.54	0.79	.406	.403	<.001***
Age (years)	-.002	-.001	.017	-0.032	.974	-0.03	0.03	.000	.399	.961
CRP peak	-.037	-.002	.003	-0.641	.522	-0.01	0.00	.001	.397	.522
Model 3: Presurgery										
MMSE	.630	.665	.063	10.609	<.001***	0.54	0.79	.406	.403	<.001***

Age (years)	-.002	-.001	.017	-0.030	.976	-0.03	0.03	.000	.399	.961
CRP rise	-.046	-.002	.003	-0.782	.435	-0.01	0.00	.002	.398	.435
Model 4:										
Presurgery										
MMSE	.633	.668	.063	10.620	<.001***	0.54	0.79	.406	.403	<.001***
Age (years)	-.002	-.001	.017	-0.040	.969	-0.03	0.03	.000	.399	.961
CRP presurgery	.042	.011	.015	0.732	.465	-0.02	0.04	.002	.398	.454
rise	-.045	-.002	.003	-0.765	.445	-0.01	0.00	.002	.396	.445
Model 5:										
Presurgery										
MMSE	.633	.669	.063	10.593	<.001***	0.54	0.79	.406	.403	<.001***
Age (years)	-.003	-.001	.017	-0.046	.963	-0.03	0.03	.000	.399	.961
CRP presurgery	.071	.019	.034	0.556	.579	-0.05	0.09	.002	.398	.454
Rise	-.035	-.002	.003	-0.508	.612	-0.01	0.01	.002	.396	.445
peak x rise	-.033	-6E-005	.000	-0.251	.802	-0.00	0.00	.000	.393	.802

Note. CRP = C-reactive Protein, MMSE = Mini-Mental State Examination; peak = highest level after operation; rise = difference between preoperative and peak level; CI = confidence interval; LL = lower limit; UL = upper limit.

*** $p < .001$.

Leukocytes. Hierarchical multiple regression models (data not shown) using age as a predictor and, separately, presurgery Leukocyte level, postsurgery Leukocyte peak, and Leukocyte rise levels yielded no model in which Leukocyte level was a significant predictor for post-operative MMSE performance. As with CRP, no models achieved significance when age was excluded from the model. Stepwise regression using the same variables did not change results, yielding only age as a predictor of pre-operative MMSE score.

Subgroup Analysis RBANS. A subgroup of 46 patients was also administered the RBANS test battery using parallel versions A and B before and six months after a heart operation. An analysis of this data to examine the associations of SIRS/Sepsis diagnosis, cytokine levels prior to operation, and the total and subtests of RBANS to test whether similar patterns as in Study 1 could be identified. Further, change in cognitive performance between the presurgery and follow-up assessment could be analyzed in this subgroup since the RBANS battery was statistically equivalent at both time points, in contrast to the MMSE versus telephone MMSE evaluations, which did not allow this. Since analyzing the change in cognition due to SIRS diagnosis or inflammatory serum biomarker parameters was the desired goal, this subanalysis employed repeated measure MMRM analysis models as in Study 1.

Continuous characteristics for the RBANS subgroup as a whole and those with and without a diagnosis of SIRS are shown in Table 33. As expected, the SIRS group (n = 5) had a longer length of stay at the ICU and more ventilator days than patients without a diagnosis of SIRS (n = 41).

Table 33

Subgroup sample sizes, means, and standard errors for continuous patient and clinical characteristics

	Total Group			No SIRS			SIRS						95% CI for Mean Difference		
Parameter	*N*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*LL*	*UL*	*Sig.*
Age (years)	46	70.74	10.17	41	70.63	10.18	5	71.60	11.23	-0.198	44	-.96	4.87	-10.78	8.85	.844
LOS Hospital (days)	46	21.85	18.20	41	18.12	11.72	5	52.40	32.28	-2.355	4.13	-34.27	14.55	-74.19	5.63	.076
LOS ICU (days)	46	4.28	5.96	41	2.80	3.17	5	16.40	9.71	-3.110	4.10	-13.59	4.37	-25.61	-1.58	.035*
BMI	44	27.29	3.97	39	27.37	4.08	5	26.64	3.26	0.385	42	.73	1.90	-3.12	4.58	.702
Ventilator (days)	46	2.05	3.08	41	1.27	1.34	5	8.42	5.64	-2.818	4.06	-7.14	2.53	-14.14	-0.14	.047*
Avg. GCS	46	5.04	4.36	41	4.45	2.86	5	9.83	10.00	-1.196	4.08	-5.37	4.49	-17.76	7.01	.297
Delirium (days)	46	0.76	1.47	41	0.76	1.52	5	0.80	1.09	-0.062	44	-.04	0.70	-1.471	1.38	.951
Surgery (Minutes)	31	261.13	96.33	27	257.59	96.92	4	285.00	102.47	-0.525	29	-27.40	52.24	-134.26	79.45	.604
GDS	46	2.04	2.31	41	2.00	2.36	5	2.40	2.07	-0.361	44	-.40	1.10	-2.64	1.84	.720
Education Years	46	12.45	3.92	41	12.17	4.00	5	14.70	2.33	-1.375	44	-2.52	1.84	-6.24	1.18	.176
Premorbid Verb. Int.	46	28.26	6.88	41	28.34	7.10	5	27.60	5.32	0.225	44	.74	3.29	-5.90	7.38	.823
MMSE pre-op	46	28.15	1.66	41	28.15	1.68	5	28.20	1.64	-0.067	44	-.05	0.79	-1.66	1.55	.946
Tel. MMSE post-op	41	19.44	2.36	38	19.53	2.17	3	18.33	4.72	0.434	2.07	1.19	2.75	-10.28	12.67	.706
RBANS pre-op	44	85.1	1.89	39	85.66	2.02	5	80.60	5.49	0.847	42	5.06	5.98	-7.01	17.14	.402
RBANS post-op	44	100.59	2.13	39	101.64	2.13	5	92.40	8.50	1.391	42	9.24	6.64	-4.17	22.65	.172

Table continues

Table 33

Subgroup sample sizes, means, and standard errors for continuous patient and clinical characteristics (Continued)

	Total Group			No SIRS			SIRS								
)Parameter	*N*	*M*	*SE*	*n*	*M*	*SE*	*n*	*M*	*SE*	*t*	*df*	*Mean Diff.*	*SE of Mean Diff.*	*95% CI for Means Difference LL*	*UL*	*Sig.*
LZ pre-op (G/L)	46	6.95	1.77	41	6.90	1.75	5	7.30	2.13	-0.468	44	-.39	0.85	-2.11	1.32	.642
post-op (G/L)	46	15.37	4.50	41	15.43	4.43	5	14.88	5.55	0.258	44	.55	2.15	-3.79	4.90	.798
rise (G/L)	46	7.70	3.62	41	7.63	3.58	5	8.33	4.33	-0.408	44	-.70	1.73	-4.20	2.79	.685
CRP pre-op (mg/L)	46	5.15	8.04	41	4.98	8.32	5	6.48	5.77	-0.389	44	-1.49	3.84	-9.25	6.26	.699
post-op (mg/L)	46	141.62	64.91	41	146.66	64.17	5	100.32	61.86	1.529	44	46.34	30.30	-14.73	107.41	.133
rise (mg/L)	46	136.48	64.06	41	141.68	62.63	5	93.84	66.29	1.604	44	47.83	29.83	-12.28	107.96	.116

Note. Independent Samples Test, 2-sided significance, equal variances assumed, alpha-level = .05. Premorbid Verbal Intelligence measured by the Wortschatz Test (WST). RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome. LOS = Length of Stay; BMI = Body Mass Index; GDS = Geriatric Depression Scale; CRP = C-reactive Protein; PCT = Procalcitonin; IL = Interleukin; LZ = Leukocyte Count; Avg. GCS = Average Glasgow Coma Scale; pre-op = preoperative; peak = highest level after operation; rise = difference between preoperative and peak level.

*$p < .05$.

Descriptive Characteristics Subgroup RBANS. Other characteristics were equivalent regardless of SIRS diagnosis. These included age, length of hospital stay, duration of delirium, comorbidities, education, cognition as measured by RBANS or MMSE, depression, or inflammatory biomarker levels, either before or after surgery. As depicted in Table 34, frequency data analysis via chi-square test showed a difference for chronic atrial fibrillation, with SIRS patients having this condition more frequently than those without SIRS.

All other parameters were equivalent across groups, including sex, mortality, pathological values of CRP and leukocytes prior to and post-surgery, and perioperative conditions. A similar pattern of CRP and LZ levels to the main cohort was also found, with around 40% having pathological CRP values before surgery and 100% having pathological CRP values post-surgery. A more dramatic shift was found for leukocytes, with less than 5% pathological prior to surgery and over 90% post-surgery. Overall, compared to the main cohort, the values of the demographic and clinical characteristics were roughly the same.

Table 34

Subgroup sample sizes, frequencies, and percent of noncontinuous patient and clinical characteristics

	Total			No SIRS			SIRS					
Parameter	*N*	*Freq.*	*%*	*n*	*Freq.*	*%*	*n*	*Freq.*	*%*	*df*	χ^2	*Sig.*
Sex (male)	46	34	73.9%	41	30	73.2%	5	4	80%	1	.108	.609
Mortality	46	0	0%	41	0	0%	5	0	0%	-	-	-
CRP Pathological												
pre-op	46	19	39,1%	41	15	36.6%	5	3	60%	1	1.026	.294
post-op	46	46	100%	41	41	100 %	5	5	100%	-	-	-
LZ Pathological												
pre-op	46	2	4.3%	41	2	4.9%	5	0	0%	1	.255	.792
post-op	46	42	91.3%	41	21	92.7%	5	4	80%	1	1.488	.233
O-H S	46	25	54.3%	41	20	51.2%	5	1	20%	1	1.488	.233
C-H S	46	21	45.7%	41	20	48.8%	5	1	20%	1	1.488	.233
O-H MS	46	7	15.2%	41	7	17.1%	5	0	0%	1	1.007	.420
CABG	46	27	58.7%	41	28	63.4%	5	1	20%	1	3.465	.085
Valve Implant	46	23	50%	41	19	46.3%	5	4	%	1	2.020	.173
Atrial Septal Defect	46	46	0%	41	0	0%	5	0	0%	-	-	-
Aortic Aneurysm Repair	46	3	6.5%	41	3	7.3%	5	0	0%	1	.391	.702
Chronic Atrial Fibrillation	46	8	17.4%	41	5	12.2%	5	3	60%	1	7.098	.031*
Chronic Pulmonary Disease	46	2	4.3%	41	1	2.4%	5	1	20%	1	3.305	.208
Heart Insufficiency	46	29	63%	41	26	63.4%	5	3	60%	1	.022	.619
Heart Infarct	46	14	30.4%	41	13	31.7%	5	1	20%	1	.289	.514
Neurological Complications	46	3	6.5%	41	2	4.8%	5	1	20%	1	1.672	.298

Note. Pearson chi-square test of homogeneity (two-sided asymptotic) for categorical data between No SIRS and SIRS, asymptotic significance testing; cases were excluded test-by-test for missing data. The pathological cut-score for CRP and Leukocytes was according to the University of Bonn Central Laboratory standards (please see Table 4 above). The pathological ranges for Leukocytes are age-adjusted and have an upper and lower cut-score. CRP = C-reactive Protein; LZ = Leukocyte Count; SIRS = Systemic Inflammatory

Response Syndrome; O-H S = Open-Heart Surgery; C-H S = Closed-Heart Surgery; O-H MS = Open-Heart Multiple Surgeries; CABG = Coronary Artery Bypass Graft.

** $p < .05$.*

Correlational Analysis. Correlation analysis is shown in Table 35, yielding slightly different results for the RBANS Subgroup compared to the main cohort. The cognitive variables (MMSE, RBANS) prior to and post-surgery were positively correlated. Aside from a negative association between peak LZ level and presurgery MMSE, no correlations were found for either MMSE or RBANS at either assessment time point and any other perioperative feature or inflammatory biomarker. This contrasts with the many negative associations with age, delirium, peak and rise values of CRP, and the lack of association with LZ level in the main cohort. Similar to the main cohort, there was no association between SIRS diagnosis and cognitive performance. SIRS diagnosis was positively associated with ventilator days only, distinctly fewer than the numerous associations with perioperative clinical features and CRP levels in the main cohort.

There was a positive correlation between the average Glasgow Coma Score (GCS) and ventilator days and the average number of delirium days and average GCS and ventilator days. There were negative correlations between peak and rise CRP levels, presurgery LZ level, and age. There was a similar negative association between peak and rise CRP levels and average GCS and delirium days. These patterns were expected. Presurgery CRP was not associated with any other inflammatory parameter, including CRP rise and CRP peak. CRP rise and CRP peak were, logically, highly positively correlated but not with any other inflammatory parameter. Leukocyte count presurgery was also not associated with any other inflammatory parameter, including the leukocyte's rise or peak. Neither leukocyte rise nor peak was associated with any other inflammatory parameter or each other.

Table 35

Subgroup correlation analysis of cognitive and serum biomarker parameters

Parameter	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
RBANS															
1. Presurgery	-														
2. Postsurgery	.573**	-													
MMSE															
3. Presurgery	.413**	.511**	-												
4. Postsurgery	.445**	.407**	.406**	-											
5. Age	.013	-.105	-.132	-.076	-										
6. BMI	-.166	-.143	-.075	-.183	-.316**	-									
7.Ventilator (days)	-.168	-.128	-.010	-.097	- .100	.132	-								
8. Avg. GCS	-.031	-.021	-.097	-.082	.213	.015	.290**	-							
9. Delirium (days)	-.065	-.165	-.088	-.163	.211	.018	.290*	.502**	-						
CRP															
10. presurgery	-.069	-.068	-.068	-.050	-.051	-.089	.201	.067	.121	-					
11. peak	-.105	.048	-.057	-.091	-.253*	.180	.006	-.292**	-.239*	.126	-				
12. rise	-.106	.032	-.070	-.109	-.249*	.219*	.003	-.290**	-.241*	.064	.942**	-			
Leukocytes															
13. presurgery	-.085	-.02	.056	.075	-.247*	.226*	.220*	.046	-.091	.122	.017	.026	-		

14. peak	-.155	-.175	-.271*	-.177	.050	.079	.108	.069	.189	-.134	-.045	-.022	-.057	-	
15. rise	-.200	-.175	-.011	.025	-.184	.219*	.147	-.050	.034	-.011	-.062	-.076	.146	.092	-
16. SIRS	-.092	-.148	.002	-.032	.029	.000	.412**	.203	.072	.173	-.148	-.124	.085	-.007	.046

Table 35

Subgroup correlation analysis of cognitive and serum biomarker parameters (continued)

Parameter	1.	2.	3.	4.	5.	6.	7.	8.	9.	1.	11.	12.	13.	14.	15.	16.	17.
16. O-H S	.130	-.057	-.020	.181	.081	-.155	.089	-.005	.057	-.181	-.127	-.090	-.060	.061	-.060	-	-
17. C-H S	-.130	.057	.020	-.181	-.081	.155	-.089	.005	-.057	.181	.127	.090	.060	-.061	.060	-.180	-
18. O-H MS	.172	.050	.148	.253	.059	.006	.070	-.045	.166	-.220	.025	.034	-.117	-.017	.173	-.148	.388**

Note. Kendall's Tau bivariate correlation analysis (2-tailed). Pairwise case deletion in case of missing. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, MMSE= Mini-Mental State Examination, BMI = Body Mass Index, Avg. GCS = Average Glasgow Coma Scale. CRP = C-reactive Protein, SIRS = Systemic Inflammatory Response Syndrome. O-H S = Open-Heart Surgery, C-H S = Closed-Heart Surgery, O-H MS = Open-Heart Multiple Surgeries.

** $p < .05$, ** $p < .01$.*

In the main analysis concerning associations between presurgery and peak levels of the same cytokine, correlation analysis yielded no correlation between presurgery and peak level of CRP, nor between presurgery and peak level of leukocyte levels. There was a positive association between presurgery level CRP and leukocytes. But no association for the peak post-surgery levels of these biomarkers.

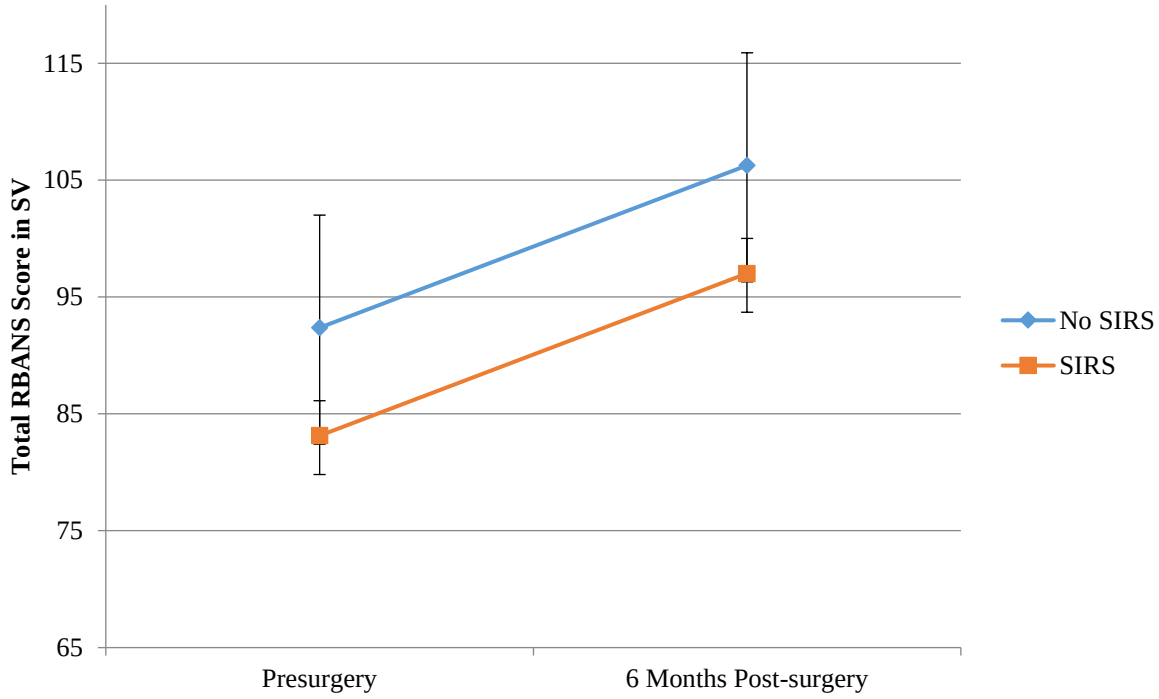
Multilevel Modelling with Repeated Measures (MMRM). Repeated measure MMRM analysis models were carried out as in Study 1, using SIRS Diagnosis, baseline and rise levels of Leukocytes and C-Reactive Protein in a series of separate models as predictors and RBANS assessments as repeated measures. This enabled the analysis of change in cognition. Using the smallest Akaike information criterion (AIC) to compare variance-covariance matrix structures for Sigma, an unstructured correlations (UN) structure was considered the best fit for each model.

Diagnosis of SIRS. MMRM analysis, including SIRS and time as predictors, yielded no significant main effect of SIRS diagnosis *(p* = .227) and no significant interaction with time *(p* = .399). There is a main effect of time *(p* < .001). Hence, SIRS does not modulate the course of the cognitive trajectory.

Figure 8 depicts changes in RBANS scores over time as estimated by MMRM by-SIRS status over the two assessment time points: for those with a SIRS diagnosis, there are 9.2 fewer points RBANS. Here, too, there was no difference in the cognitive trajectory due to diagnosis of SIRS, both groups having around -1.5 SD below the norm of 100 points prior to surgery, and both improving by 11.8 points (a little more than +1 SD) at the second assessment six months post-surgery.

Figure 8

RBANS by SIRS based on MMRM estimates of means



Note. SIRS did not have a main effect. Total RBANS in Standard Values. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SIRS = Systemic Inflammatory Response Syndrome; SV = Standard Values.

Due to wide standard errors, there was no significant main effect of SIRS diagnosis. The magnitude of the estimated effect of SIRS diagnosis can be taken from the parameter estimate shown in Table 36. It should be noted that the reference category for this analysis was patients without a diagnosis of SIRS.

Table 36

Subgroup summary of estimates of fixed parameters from separate MMRM Analyses of SIRS

Model	*Estimate*	*Std. Error*	*df*	*t*	*Sig.*	95% CI	
						LL	UL
SIRS Diagnosis	9.24	6.644	42	1.391	.172	-4.16	22.64

Note. Diagnosis of "No SIRS" is the reference category. SIRS = Systemic Inflammatory Response Syndrome. These are fixed parameter estimates for the main effect of SIRS; CI = confidence interval; LL = lower limit; UL = upper limit.

CRP. The results of the Type III tests of fixed effects for the RBANS using CRP presurgery, rise or peak values are given in Table 37, including the interaction with time, denoted "change over time," as well as the goodness of fit measure AIC for Model 4 and 5 for purposes of comparison.

The presurgery CRP (Model 1) and peak CRP values (Model 3) each showed a main effect, but not the rise of CRP alone (Model 2). The entry of both presurgery and rise in CRP in the same model (Model 4) yielded a main effect for both parameters. This model also had the best fit of any model analyzed, according to the smallest AIC. Model 5, based on Model 4 but included an interaction term between presurgery and rise levels, yielded no significant effects.

Table 37

Subgroup summary of separate MMRM Analyses of CRP predictors of RBANS

	Main Effect	Change over Time	
MMRM Model	*Sig.*	*Sig.*	
1. Presurgery	.927	.098	
2. Rise	.794	.240	
3. Peak	.805	.172	
4. Combined			AIC
Presurgery	.918	.109	**682.136**
Rise	.792	.263	
5. Combined with interaction term			
Presurgery	.027	.109	685.000
Rise	.059	.263	
Presurgery x Rise	.019*	-	

Note. These are the p-values for the main effect as estimated by the sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. CRP = C-reactive Protein. Rise: Peak level post-surgery minus presurgery level; AIC = Akaike information criterion.

* $p < .05$.

The parameter estimates of each model are reported in

Table 38 and estimate the influence on cognition at each time point. There were two main effects in Model 5, with presurgery and the interaction term presurgery*rise being significant. There was no interaction with time for either presurgery or rise values in Model 5. Hence, for every ten mg/L of presurgery CRP level, the estimated fixed effect was 16 fewer RBANS points (i.e., approximately 1.5 SD below the norm). The interaction between presurgery and rise indicated that for every 100 unit increase in this interaction, there was a lower RBANS score by 1.3 points. Model 5 also had the smallest AIC, indicative of a better model fit than Model 4.

Table 38

Subgroup summary of estimates of fixed parameters of MMRM analyses of CRP predictors of RBANS

	Parameter	*Estimate*	*SE*	*df*	*t*	*Sig.*	95% CI *LL*	95% CI *UL*
1.	Presurgery	.180	.265	42	0.469	.501	-0.36	0.72
2.	Rise	.006	.033	42	0.197	.845	-0.06	0.07
3.	Peak	.009	.032	42	.277	.783	-0.06	0.08
4.	Combined							
	Presurgery	.178	.269	41.00	0.662	.512	-0.37	0.72
	Rise	.005	.034	41.00	0.163	.871	-0.06	0.07
5.	Combined with interaction term							
	Presurgery	-1.649	.788	42.278	-2.074	.044*	-3.23	-0.04
	Rise	-.064	.043	46.607	-1.495	.142	-0.15	0.02
	Presurgery x Rise	.013	.005	40.000	2.435	.019*	0.01	0.02

Note. These are fixed parameter estimates based on REML (Restricted Maximum Likelihood). CRP = C-reactive Protein. . RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

Leukocytes. A main effect was found for leukocyte rise (Model 2), but no main effect for presurgery or peak (Models 1 and 3, see

Table 39). The combined models showed an effect of rise only in Model 4 (no interaction term between presurgery and rise). However, Model 5, which had the best fit, according to AIC, showed three main effects: presurgery and rise levels and an effect of their interaction. In none of the models examined was there an interaction with time.

Table 39

Subgroup summary of MMRM analyses of Leukocytes predictors of RBANS

	Main Effect	Change over Time	
MMRM Model	*Sig.*	*Sig.*	
1. Presurgery	.916	.806	
2. Rise	.009*	.583	
3. Peak	.165	.765	
4. Combined			AIC
Presurgery	.654	.859	660.742
Rise	.009*	.605	
5. Combined with interaction term			
Presurgery	.003*	.859	**651.258**
Rise	.016*	.605	
Presurgery x Rise	.001*	-	

Note. These are the p-values for the main effect as estimated by sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time. Rise: Peak level post-surgery minus presurgery level. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; AIC = Akaike information criterion.

* $p < .05$.

As shown in Table 40, there was an inconsistent pattern of main effects across models. There was an expected negative parameter estimate of rise in Model 2 such that for a 10 G/L increase in Leukocyte level, the RBANS score was lower by 17.7 points.

Although this was not statistically significant, a similar pattern was shown for the simple peak model (Model 3). The combined model (Model 4) also showed the expected direction of association between rise and cognition such that a 10 G/L was associated

with a 12.9-point fewer points in RBANS score. Counterintuitively, the better-fitting model, which

Table 40

Subgroup summary of estimates of fixed parameters of MMRM analyses of Leukocyte predictors of RBANS

	Parameter	Esti-mate	SE	df	t	Sig.	95% CI Lower Bound	95% CI Upper Bound
1.	Presurgery	.221	1.214	42.00	0.182	.856	-2.23	2.67
2.	Rise	-1.777	.561	42.00	-2.097	.042*	-2.31	-0.04
3.	Peak	-.522	.469	42.00	-1.113	.272	-1.47	0.42
4.	Combined							
	Presurgery	.529	1.176	41	0.450	.655	-1.85	2.90
	Rise	-1.209	.571	41	-2.116	.040*	-2.36	-0.06
5.	Combined with interaction term							
	Presurgery	4.620	1.577	48.03	2.934	.005**	1.46	7.80
	Rise	4.073	1.595	42.65	2.554	.014*	.86	7.29
	Presurgery x Rise	-.718	.205	40.00	-3.498	.001**	-1.13	-0.30

Note. These are fixed parameter estimates based on REML (Restricted Maximum Likelihood). RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; CI = confidence interval; LL = lower limit; UL = upper limit.

** p < .05. ** p < .01.*

included an interaction term between presurgery and rise levels, yielded a positive association between presurgery and rise levels and cognition. For each parameter individually, a 10 G/L increase leads to a dramatic rise of more than 40 points in the

RBANS score. However, the interaction term yielded 7.1 fewer points in RBANS score for each 10 G/L rise in leukocyte level.

Discussion

Pathology levels. The two inflammatory biomarkers examined in Study 2 indicated large shifts from over half of patients having had normal levels of CRP prior to heart surgery to an overwhelming majority with pathological values in CRP levels after surgery. Unlike Study 1 for leukocytes, in Study 2, this pattern also held for leukocyte levels: over 90% had normal leukocyte levels prior to heart surgery, shifting completely around over 90% having pathological (raised) leukocyte levels.

Differences in Biomarkers across SIRS Diagnostic Groups. In Study 2, diagnosis of SIRS went hand in hand with higher peak and rise levels of CRP after surgery and higher rise levels of leukocytes in the large study analysis. However, the subgroup of patients who also had additional testing (beyond just MMSE) did not show this pattern. There were no differences in biomarker values concerning the presence or absence of SIRS. This may be why so little could be detected in the subgroup analyses of study 2 using hierarchical regression analyses of RBANS.

Hypothesis 1: Are higher levels of chronic inflammation associated with indicators of acute inflammation. In the main analysis, there was no association between presurgery and peak level of CRP, nor between presurgery and peak level of leukocyte count. As expected, there was a positive association between presurgery level CRP and presurgery Leukocyte count. Presurgery levels of either CRP or leukocytes did not associate with the clinical diagnosis of SIRS. Similarly, presurgery CRP was not associated with any other inflammatory indicator in the subgroup analysis, including CRP rise and CRP peak. Leukocyte count presurgery was also not associated with other inflammatory parameters, including the leukocyte's rise or peak. Hence, presurgery levels

of CRP and Leukocytes, which served as proxies for chronic inflammation in this study, were not associated with post-surgery acute inflammation or post-surgery diagnosis of systemic inflammatory response in this cohort. Previous studies of leukocyte infiltration or CRP recruitment in chronic inflammatory conditions and associated mechanisms of acute inflammation show differing effects, depending on the precise model used. It has, for instance, been demonstrated that chronically inflamed tissue may change the underlying mechanisms and the degree of acute inflammatory responses (Ma et al., 2016). The lack of such an association in this cohort may be due to the constraints of having no healthy controls and hence, less variance. Alternatively, the level of chronic inflammation was non-pathological and, hence, potentially unable to alter inflammatory mechanisms.

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance at any time point. The presurgery global cognitive score measured by MMSE was not associated with either inflammatory marker or SIRS in simple correlation or multiple regression analysis. Further, postsurgery global cognition (21-item telephone version of MMSE) was negatively associated with peak and rise levels of CRP, but not Leukocytes or SIRS diagnosis in correlational analysis. Further hierarchical regression analyses, including the 30-point presurgery MMSE as a regressor, did not yield a meaningful model using CRP, Leukocyte levels, or SIRS diagnosis.

A closer examination of cognition in the auxiliary group of heart surgery patients who received RBANS yielded no main effect of SIRS diagnosis. Using MMRM models, however, it could be shown that presurgery CRP and peak CRP had a negative effect on the total RBANS score. In addition, both presurgery CRP and rise of the same model yielded a main effect for both parameters, and this model had the best fit. In other words, there appeared to be an estimated lowering of RBANS score by 16 points for every 10 mg/L increase in presurgery CRP level. Three main negative effects for leukocyte

presurgery and rise levels, as well as an effect of their interaction, were found using MRMM analysis. In none of the models examined was there an interaction with time.

Hypothesis 3: Do chronic and acute systemic inflammation influence the trajectory of cognitive performance over time? MRMM analysis did not yield an interaction between SIRS and time, indicating that SIRS did not associate with cognitive trajectory. The same was found for either presurgery or rise values of CRP or any leukocyte parameter. The fact of no time-varying change over time means there is no difference in the slope of cognitive performance according to the level of inflammatory biomarkers or SIRS diagnosis.

Hypothesis 4: Is there an interaction between chronic and acute inflammation on cognitive performance? The presurgery levels of leukocytes did not moderate the effects of acute inflammation on cognitive performance since the interaction terms of presurgery and postsurgery rise, or peak levels were not significant. There was a negative effect of the interaction term of presurgery and rise level of CRP on the RBANS score, in which a small reduction in the RBANS score of 1.3 points was found for every 100 unit increase of the interaction term.

Limitations of this study include the relative imprecision of MMSE and its shortened telephone variant in the main cohort, despite a relatively large sample size, the comparatively small sample size, and concomitant potential selection bias in the subgroup who received extensive cognitive testing. It may be that those who made themselves available for more extensive testing could have been healthier or otherwise have been motivated to be tested due to worry or particular confidence about cognitive ability. Additionally, there was some attrition in the main cohort, perhaps due to mortality or greater disease.

It could be that disease severity, age, and experience of delirium could explain cognitive outcomes better. In addition, acute cardiac events, vascular risk factors, previous cardiac events, inflammaging, and psychiatric burden may have contributed to presurgery inflammation and a worsening of cognitive performance either prior to or after surgery.

An additional issue is the direction of causality of inflammation negatively influencing cognition or, perhaps instead, the other way around remains unanswered. Bidirectionality has been indicated in previous research (Shah et al., 2013a).

Study 3. General Operative Patients

In this examination nested within a larger study of sepsis (blood poisoning), a further examination of the original hypotheses was conducted among a sample of major surgery patients, most of whom underwent cardiac surgery, and all of whom spent at least one day at the intensive care unit for monitoring (Widmann et al., 2013). This study assessed a wider panel of serum inflammatory biomarkers among post-operative patients who underwent similar cognitive investigations before and after surgery. Here, it was expected that those patients with higher levels of presurgery inflammation would also have higher levels of acute inflammation. The question was whether the findings in studies one and two could also be supported here.

Hypotheses

The main questions in this study were the same as in the preceding studies:

Hypothesis 1: Are higher chronic inflammation levels associated with acute inflammation indicators?

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance at any time point?

Hypothesis 3: Do chronic and acute systemic inflammation influence the trajectory of cognitive performance over time?

Hypothesis 4: Is there an interaction between chronic and acute inflammation on cognitive performance?

Specifically, Study 3 employed the most extensive cognitive testing and biomarker parameters. This study enabled close examination of biomarkers from different perspectives, i.e., comparable to those of Study 1 to a very limited extent and comparable to Study 2 in the methodology. Cognition was examined in detail together with biomarkers of inflammation using similar models to those in Studies 1 and 2.

Methods

Recruitment.

All patients scheduled for major surgery from September 2013 through December 2016 were consecutively screened at the premedical stage of the Department of General Surgery and Department of Orthopedic Surgery in collaboration with the Anesthesiology Department at the University Hospital Bonn. Since this was part of an ongoing study still in the recruitment stage, 31 major surgery patients were included in this analysis. They were scheduled for a planned major operation, not necessarily due to coronary heart disease or heart valve failure.

Inclusion criteria were age between 25 and 80 years old, German-speaking, scheduled elective or urgent major surgery, admitted to the intensive care units of the Anesthesiological-Operative Intensive Care Unit of the University Hospital Bonn, which includes a surgical ICU, an anesthesiological ICU, and a cardio-surgical ICU, duration of ICU stay for a minimum of 24 hours. In case of transfer to intermediate care or the observation ward before the 24-hour ICU period is complete, study parameters must be allowed to be assessed—lastly, an MMSE score of 25 or more.

Exclusion criteria were non-German speaking patients, simultaneous participation in any clinical treatment study involving administration of an investigational medicinal product within 30 days prior to inclusion; physical or psychiatric condition which at the investigator's discretion may put the subject at risk, may confound the study results, or may interfere with the subject's participation in this study; prior to the start of this study existence of preexisting severe diseases and/or conduction of surgery necessarily imply life expectancy less than 12 months; known or suspected persistent abuse of medication, drugs or alcohol now or in the past; known cerebral lesions, cerebral infarction or malignoms, dementia or history of other CNS diseases; Cranio-cerebral injury; known

HIV-Infection; known liver cirrhosis with a documented Child-Pugh Score of C prior to this study (Indication of Liver Disease; Pugh, Murray-Lyon, Dawson, Pietroni, & Williams, 1973); liver transplants; prior to the start of this study nursing care level of 2 or 3 *(German: "Pflegestufe 2 oder 3");* residing in a nursing home prior study start.

Ethical Considerations.

This study protocol was reviewed by the Medical Ethics Review Board of the University Hospital Bonn (IRB Number 270/21) and the Medical Ethics Review Board of the Ärztekammer Nordrhein (IRB Number 2/2016/108881; Widmann et al., 2013). The study was conducted in accordance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) for Good Clinical Practice and the relevant national regulations and the Declaration of Helsinki (General Assembly of the World Medical Association, 2014), as laid out in the Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16, 2014, on clinical trials on medicinal products for human use (European Parliament, Council of the European Union, 2014). In addition, local ethical research guidelines and research guidelines of University Hospital Bonn (Regulations for ensuring good scientific practice; (Der Rektor der Rheinischen Friedrich-Wilhelms-Universität Bonn, 2021) and the European General Data Protection Regulation (EU) 2016/679 were applied (Publications Office of the European Union, 2016).

This study is registered at the International Clinical Trials Registry Platform of the U.S. National Library of Medicine "ClinicalTrials.gov" (primary registry trial identifier: NCT02339649; first registration date: January 15, 2015, cross-referenced at the World Health Organization International Clinical Trials Registry Platform).

This study was conducted exclusively by trained and qualified medical investigators, psychologists, and study nurses who had current Good Clinical Practices certifications.

Data Protection and Subject Confidentiality.

The pertinent provisions of the Germany-specific legislation on data protection were fully complied with. The collection, transmission, archiving, and evaluation of personal data in this study were performed according to local laws (Data Protection Act). Before study participation, each subject was informed by the investigator about the purpose and extent of data collection and use of personal data, particularly medical data. All participants gave written informed consent.

Financial Considerations.

The study was fully funded by the German Center for Neurodegenerative Diseases (DZNE). All subjects were reimbursed 50 EUR per visit throughout the study.

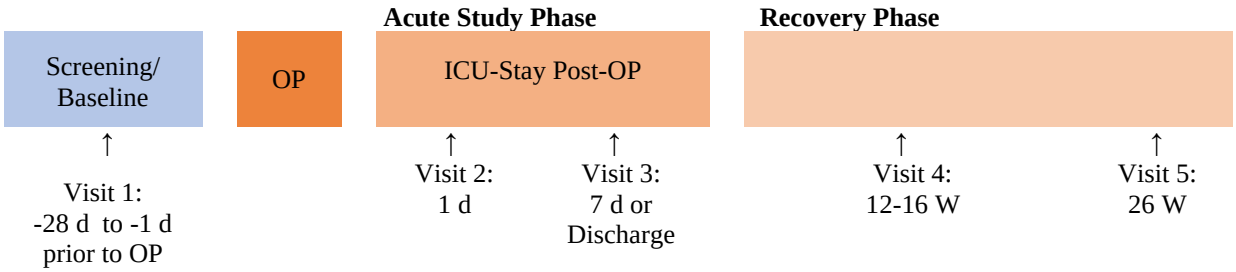
Study Procedure.s

There was a total of 5 study visits in this study, as shown in

Figure 9. Brief cognitive assessments based on the MMSE were conducted at three points: at least one day before surgery (“Pre-OP”), 3-4 months post ICU, and six months later. After a recovery period of 6 months post-ICU follow-up, there was a comprehensive neuropsychological examination.

Figure 9 Study Phases and Timing of Visits

Study Phases and Timing of Visits



Note. OP = Operation/Surgical Procedure, ICU = Intensive Care Unit, d = day, W = week.

Cognitive Assessment

The pre-operative MMSE was conducted at the Surgery Department of the University of Bonn Medical Center. Post-ICU follow-up neuropsychological assessments occurred at the German Center for Neurodegenerative Diseases (DZNE), Center for Clinical Research, Bonn.

The *Mini-Mental Status Examination* (Folstein, 1975) was used as a screening instrument prior to study inclusion and at each post-ICU follow-up assessment. A comprehensive test battery was conducted at the six- and twelve-month follow-ups.

Table 41 lists specific assessments and inventories used. The six-month assessments also included a series of scales covering depression, somatic symptoms, anxiety, and posttraumatic stress.

Table 41

List of neuropsychological assessments, inventories, and questionnaires

Cognitive Domain	Assessment Name
Cognitive Screening	Mini-Mental Status Examination (MMSE)
Verbal Memory	Verbal Learning Memory Test (VLMT)
Visual Memory	Wechsler Memory Scale Visual Recall I and II (VR I&II)
Working Memory	Wechsler Memory Scale Subtest Digit Span
Premorbid Verbal Ability	German Vocabulary Test Mehrfachwahl-Wortschatztest-B (MWT-B)
Cognitive Speed	Symbol Digit Modalities Test (SDMT)
Simple and Divided Attention	Trail Making Test A & B (TMT A&B)
Verbal Fluency	Subtests formal lexical memory (“S”) and semantic verbal fluency (“Animals”)
Depression and Somatic Psychiatric Inventory	Patient Health Questionnaire (PHQ-D) Subtests Depression and Somatic Symptoms
Anxiety Inventory	Becks Anxiety Inventory (BAI)
Post-Traumatic Stress Disorder Screening	Post-Traumatic Stress Syndrome 10 Questionnaire (PTSS-10)

Demography, Comorbidities, Perioperative Parameters

Age, sex, body-mass index, mortality, and clinical parameters included type of surgery, length of surgery, mortality, SIRS Diagnosis, neurological complications, ventilator days, delirium days, Glasgow coma scale (GCS), which was averaged for the time during ICU stay, Geriatric Depressions Scale, length of stay at the hospital and the intensive care unit and thrombocytes (10*3/mm³), and several intensive care clinical scales, as listed in Table 42. . Lastly, the ejection fraction (EF), a measure of heart insufficiency, was also included as a fixed effect in the cognitive data analysis.

Table 42

Clinical scales from the perioperative period

Scale	Abbreviation	Purpose/Area of application
Acute Physiology and Chronic Health Evaluation	APACHE II	Estimation of mortality
Therapeutic Intervention Scoring System-10	TISS-10	Illness severity rating
Simplified Acute Physiology Score	SAPS II	The severity of disease in the first 24 hours of a patient's stay at intensive care units
Sequential Organ Failure Assessment*	SOFA	A rating scale for the degree of dysfunction/failure
Confusion Assessment Method for the ICU*	CAM-ICU	Delirium assessment

Note. The modified SOFA scale is described in the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3, Singer, et al., 2016)

Proinflammatory Serum Biomarkers

Blood samples were drawn before cardiac surgery as part of the presurgical work-up and as medically indicated at several points in the post-surgery period. Proinflammatory biomarkers included were Leukocytes (gL) and C-Reactive Protein (mg/L). The presurgical and maximum value of Leukocytes and CRP in the postsurgery period derived from patient files post-hoc were also used for analyses requiring dynamic information.

Blood chemistry was determined in collaboration with the Central Laboratory at the Bonn University Hospital Institute for Clinical Chemistry and Clinical Pharmacology, Bonn, and the German Center for Neurodegenerative Diseases (DZNE), Biomarker Dementia Working Group, Bonn.

Statistics and data analysis

Dropouts

There were many dropouts among the patients included in the operative arm of the study, as depicted in Missing data Analysis

Missing value analysis among those who had cognitive and biomarker data at Visit 5 was conducted using SPSS 22.0, as recommended in Tabachnik and Fidell (2007), including estimation of means and t-tests, as well as evaluations of the pattern of missing data (Appendix D). In total, of the 31 participants who were assessed, some of the missing cytokine data were merely due to the differences in lengths of stay at the intensive care unit. Some were missing for specific assessment days, which varied across cytokines and cognitive assessments (up to as many as 5 to 7 participants of the total sample of 31, Appendix D. For this reason, these data were dealt with via case-wise deletion in correlation analysis but otherwise not used for further analytical steps. Instead, the post-hoc CRP and LZ values were used. Some other data points (delirium, SAPS2-Score, ventilation days had missing data above the 10% threshold. These parameters were not used in any data analysis, and no data was imputed for these values (Appendix D).

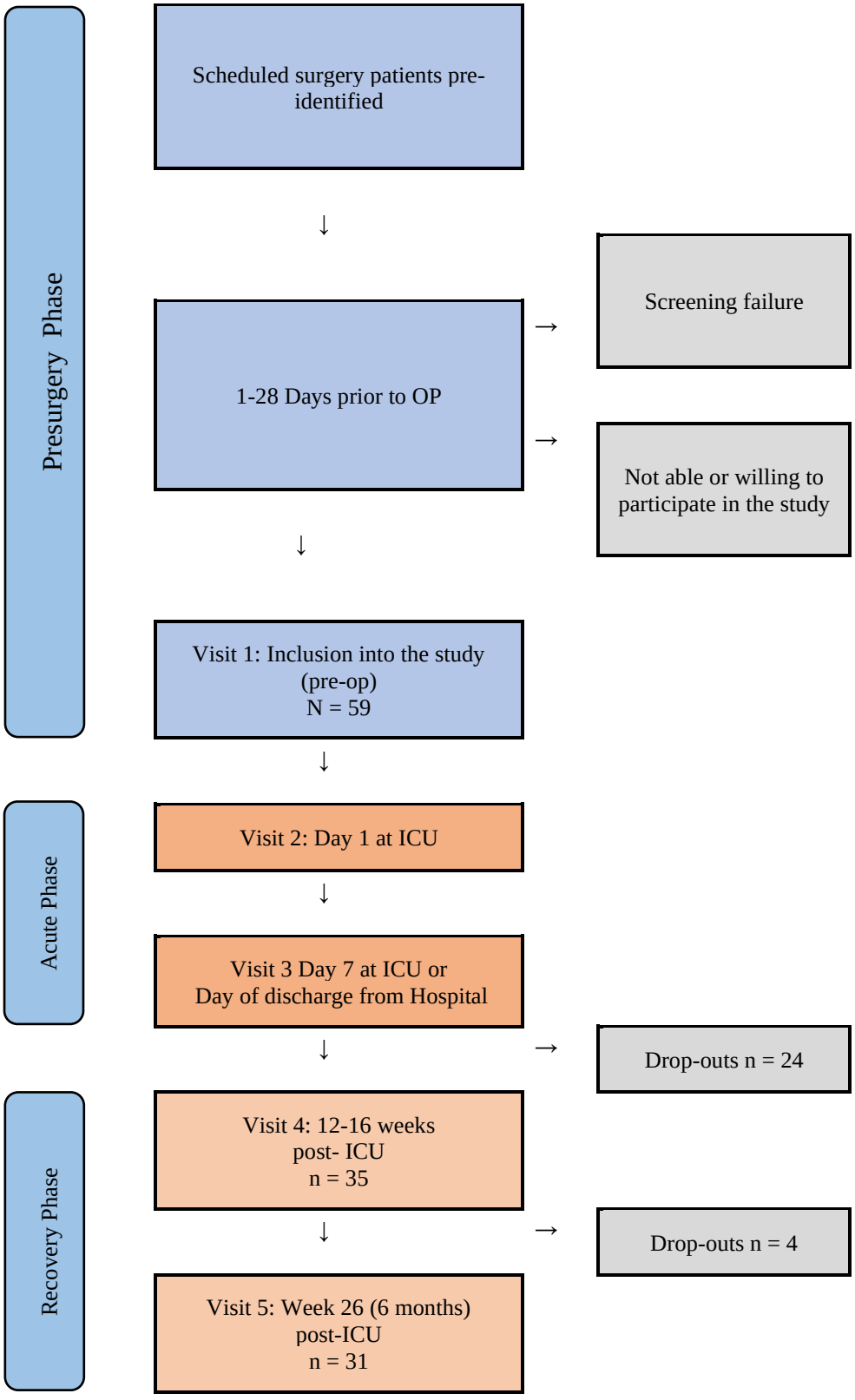
Figure 10. Of the 59 initially included in the study, only 31 remained for analysis at Visit 5. For this analysis, only those who remained in the study until Visit 5 were included in the analysis of long-term cognition.

Missing data Analysis

Missing value analysis among those who had cognitive and biomarker data at Visit 5 was conducted using SPSS 22.0, as recommended in Tabachnik and Fidell (2007), including estimation of means and t-tests, as well as evaluations of the pattern of missing data (Appendix D). In total, of the 31 participants who were assessed, some of the missing cytokine data were merely due to the differences in lengths of stay at the intensive care unit. Some were missing for specific assessment days, which varied across cytokines and cognitive assessments (up to as many as 5 to 7 participants of the total sample of 31, Appendix D. For this reason, these data were dealt with via case-wise deletion in correlation analysis but otherwise not used for further analytical steps. Instead, the post-hoc CRP and LZ values were used. Some other data points (delirium, SAPS2-Score, ventilation days had missing data above the 10% threshold. These parameters were not used in any data analysis, and no data was imputed for these values (Appendix D).

Figure 10 Flow chart of recruitment, visits

Flow chart of recruitment, visits



Tests of normality of data distribution

P-P plots of residuals were visually examined for all cognitive variables (Appendix D). The two MMSE scores at Visit 1 and Visit 5 were normally distributed. VLMT Trials 5, 6, 7, and recognition tasks were normal. TMT-A and –B, semantic verbal fluency, and digit span were near normal.

Correlation Analysis

Bivariate Pearson correlation of cognition and biomarker data, chi-square tests of frequency and ordinal data, and independent sample 2-sided student T-Tests were conducted for continuous descriptive data. Kendall's Tau correlation was used for nonparametric data.

Results

Descriptive Characteristics

The therapeutic and intensive medical scales indicate the general level of health of the patients in this cohort. Frequencies of patient characteristics, percentages of demographic and clinical conditions, and non-continuous intensive care clinical scores are shown inTable 43. Patients in this study were, on average, 65.5 (SE 1.43) years of age and predominantly male (N = 31, female 9/31, 29%). The average years of education were moderate at 13.4 (SE .5). The average length of hospital stay of 12.6 days (SE 1.8d) and ICU stay of 4.86 days (SE .85) were relatively long.

Table 43

Sample sizes, means, standard errors, and standard deviations for continuous demographic and clinical characteristics

Parameters	*N*	*Minimum*	*Maximum*	*M*	*SE*	*SD*
Age (years)	31	43	78	65.55	1.433	7.978
Education (years)	31	8	19	13.45	.506	2.815
LOS Hospital (days)	29	2	42	12.62	1.807	9.734
LOS ICU (days)	29	0	21	4.86	.818	4.406
BMI	31	13.15	50.83	27.98	1.908	10.628
Surgery (Minutes)	31	42	520	368.55	16.578	92.30
SAPS 2 Score (Visit 2 ICU)	22	7	39	21.36	1.753	8.220
Glasgow Coma Score (Visit 2 ICU)	28	3	15	8.96	1.086	5.744
Ventilator (days)	26	1	6	1.88	.210	1.071

Note. ICU = Intensive Care Unit, BMI = Body Mass Index, SAPS 2 = Simplified Acute Physiology Score, CAM-ICU = Confusion Assessment Method – ICU.

The estimated mortality rate within 24h at the ICU of between 21.36% (SAPS-2 is on a scale of 0-100% predicted mortality). The actual mortality rate of this sample was, in fact, 0%. The average Glasgow Coma Score of 8.96 indicated a moderate estimated level of consciousness. No one in this cohort suffered from delirium. There was an average of less than two ventilator days.

As shown in Table 44, a very small number of patients met the criteria for the diagnosis of systemic inflammatory response syndrome (SIRS 4/ 31, 13%). All patients had elective, scheduled surgeries. The types of surgeries comprised mostly aortocoronary bypasses (15/31, 48.4%), valve implants (12/31, 38.7%), and other surgery, i.e., large stomach surgery (1/31, 3.2%). Six patients (19.4%) had more than one surgery. The most frequent reasons for surgery included, in order of frequency, hyper intensive heart disease (more than two-thirds), aortic valve stenosis (almost half), arterial hypertension

(approximately one-third of patients), and left ventricular failure (around a quarter of patients). Other conditions, according to frequency, included 41% hyperlipidemia, a third with diabetes type 2. None had a stroke, and none had liver disease.

Table 44

Sample sizes, frequencies, percentages, mode for noncontinuous patient, and clinical characteristics

Parameters	*N*	*Freq.*	*%*
Sex (male)	31	22	70.9%
Mortality	31	0	0.0%
Elective Surgery	31	31	100%
Aortocoronary Bypass	31	15	48.4%
Valve Implant	31	12	38.7%
Other Surgery	31	1	3.2%
Multiple Surgeries	31	6	19.4%
SIRS	31	4	13.3%
Stroke	31	0	0.0%
Thyrotoxicosis	31	4	13.3%
Diabetes Type 2	31	9	29.0%
Delirium	20	0	0.0%

Note. Other surgeries included Endarterectomy and explorative laparotomy, abdominal occlusion, lavage, and meshwork. Delirium assessed per CAM-ICU = Confusion Assessment Method for the ICU, SIRS = Systemic Inflammatory Response.

Serum biomarker levels determined in this study are listed for individual visits in Table 45. There were very uneven numbers of blood samples taken at the established study time points, hence a range of 1 to 21 samples at any given time point.

Table 45

Descriptive statistics for study-based serum cytokines

Parameters	*N*	*Minimum*	*Maximum*	*M*	*SE*	*SD*
CRP [mg/l]						
Presurgery	21	0.50	18.00	3.43	0.865	3.964
Day 1 ICU	19	1.30	300.00	122.23	19.449	84.777
Day 7/Discharge ICU	1	19.00	19.00	19.00		
Procalcitonin [µg/l]						
Presurgery	21	0.03	0.11	0.06	0.004	0.020
Day 1 ICU	19	0.08	2.17	0.64	0.134	0.586
Day 7/Discharge ICU	1	0.30	0.30	0.30		
IL-6 [pg/ml]						
Presurgery	21	2.00	14.50	4.17	0.719	3.293
Day 1 ICU	19	11.30	712.00	123.53	35.444	154.497
Day 7/Discharge ICU	1	32.80	32.80	32.80		
Leukocytes [G/l]						
Day 1 ICU	24	5.82	17.43	10.23	0.684	3.350
Day 7/Discharge ICU	2	8.86	10.23	9.55	0.685	0.969
NSE [ng/ml]						
Presurgery	21	5.30	29.30	12.00	1.058	4.847
Day 1 ICU	19	9.30	30.60	18.26	1.678	7.313
Day 7/Discharge ICU	1	16.50	16.50	16.50		
S100 [µg/l]						
Presurgery	21	0.03	0.10	0.06	0.004	0.019
Day 1 ICU	19	0.04	0.46	0.16	0.025	0.109
Day 7/Discharge ICU	1	0.05	0.05	0.05		

Note. CRP = C-Reactive Protein; IL-6 = Interleukin-6; NSE = Neuron-specific enolase; S100 = calcium-binding protein; ICU = Intensive Care unit.

The frequencies of abnormal (pathological) values of the serum biomarkers are found in Table 46 only for the baseline presurgery visit. Too few data points were collected to state what proportion of patients had pathological values and how this shifted post-surgery. Therefore, to assess the *dynamic* process underpinning the development of acute systemic inflammation, the patient files were drawn upon to obtain the lowest presurgery CRP and leukocyte values and peak CRP and leukocyte values while in the ICU (as in Study 2). In addition, leukocyte count was not assessed prior to surgery for the BonSEP study. Therefore, the second set of presurgery and post-surgery values for CRP and leukocytes (LZ) was generated from patient files *post hoc*, as was done for Study 2, in the perioperative period.

Table 46

Descriptive statistics pathological status at baseline of proinflammatory biomarkers

Biomarker	Normal *Freq. (%)*	Pathological *Freq. (%)*	Missing *Freq. (%)*
CRP [mg/l]	12 (35.3%)	8 (23.5%)	14 (41.2%)
LZ [G/l]	0 (0%)	0 (0%)	31 (100%)
PCT [µg/l]	20 (58.8%)	0 (0%)	14 (41.2%)
IL-6 [pg/ml]	20 (58.8%)	0 (0%)	14 (41.2%)
NSE [ng/ml]	13 (38.2%)	7 (20.6%)	14 (41.2%)
S100 [µg/l]	20 (58.8%)	0 (0%)	14 (41.2%)

Note. Reference ranges and clinical designations derived from the internal documents for each biomarker at University Hospital Bonn Central Laboratory's intranet website: http://www.meb.uni-bonn.de/klinbiochem/laborbuch November 27, 2016. CRP = C-reactive Protein; LZ = Leukocyte Count; PCT = Procalcitonin; IL-6 = Interleukin-6; NSE = Neuron-specific enolase; S100 = calcium-binding protein.

The average number of days of the patient-file-based CRP before surgery was *M (SD)* 2.7 (2.11) days and 3.6 (2.32) days after surgery. The patient file leukocyte determination before surgery was an average of 2.6 (2.11) days before and 2.8 (2.77) days after surgery. As shown in Table 47, there was an average rise in CRP of 19.2 mg/l of blood and a rise in LZ of 8.13 G/l of blood. Hence there was a clear, dynamic change in these biomarkers rendering far CRP and LZ values pathological for both measures in the post-operative period. Since LZ values can also shift downward, it should be noted that the number of low-pathological values of LZ in the presurgery phase was 1 (2.9%) prior to surgery and 0 (0%) post-surgery. Further descriptive statistics for cognitive and psychological scales are given in Table 48 and Table 49.

Table 47

Descriptive statistics of patient-file derived CRP and LZ values

Parameters	N	Minimum	Maximum	M	SE	SD	Frequency Patho-logical (%)
CRP pre-op	31	0.30	12.20	2.99	3.023	0.543	11 (35.3%)
peak	31	19.50	244.00	152	53.033	9.525	28 (91.2%)
rise	31	19.20	239.60	149.02	53.106	9.538	
LZ pre-op	31	3.44	10.10	7.00	1.615	0.290	1 (2.9%)
peak	31	8.43	28.14	13.74	4.087	0.734	22 (70.6%)
rise	31	1.29	19.94	6.73	3.978	0.714	

Note. Low and high pathological values were age-based 18-64 years LZ <3.9 G/L or >10.2 G/L; ≥65 years LZ<3.6 G/L or >10.5 G/L. CRP > 3 mg/l pathological. Source of reference values internal documents for each biomarker at University Hospital Bonn Central Laboratory's intranet website: http://www.meb.uni-bonn.de/klinbiochem/laborbuch November 27, 2016. CRP = C-reactive Protein; LZ= Leukocyte Count.

Table 48

Sample sizes, range, means, and standard errors and deviations for cognitive data

Parameters	*N*	*Minimum*	*Maximum*	*M*	*SE*	*SD*
MWT-B	31	16	35	29.74	.869	4.837
MMSE						
pre-op	31	26	30	29.23	.195	1.087
3-4 Months post-op	31	26	30	29.94	.207	1.153
6 Months post-op	31	26	30	29.03	.194	1.080
VLMT						
Learning	31	17	60	41.06	1.868	10.399
Immediate Recall	31	0	13	6.71	.626	3.485
Delayed Recall	31	1	13	7.23	.606	3.374
Recognition	31	6	15	12.06	.412	2.294
WMS-IV						
Visual Reproduction I	30	17	43	33.57	1.136	6.224
Visual Reproduction II	30	11	43	26.60	1.724	9.445
Recognition	29	0	7	5.69	.302	1.628
WMS-R Digit Span						
Forwards	31	4	10	7.06	0.324	1.806
Backwards	31	2	11	5.61	0.346	1.927
RWT Verbal Fluency						
Phonetic	31	9	44	22.06	1.237	6.889
Semantic	31	5	24	11.35	.862	4.800
Trail Making Test						
TMT A	31	20	81	46.26	2.654	14.776
TMT B	31	39	296	116.87	11.755	65.447
SDMT Correct Answers	31	19	72	45.03	2.177	12.123

Note. MWT-B = Mehrfachwahl Wortschatztest (Vocabulary Test); VLMT = Verbal Learning and Memory Test; WMS-IV = Wechsler Memory Scale IV; WMS-R = Wechsler Memory Scale- Revised; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test; RWT = Regensburger Word Fluency Test.

Table 49

Sample sizes, range, means and standard errors, deviations frequencies for psychiatric scales

Parameters	*N*	*Minimum*	*Maximum*	*M*	*SE*	*SD*
Beck's Anxiety Inventory	31	0	31	7.42	1.660	9.240
PTSS-10	31	10	46	17.84	1.542	8.583
PHQ-D						
Soma	31	0	17	4.03	.706	3.928
Depression	31	0	13	3.87	.662	3.685
Experiences at ICU	*N*	Freq.	%			
Nightmares/Hallucinations	31	8	25.8%			
Severe Anxiety or Panic	30	3	10.0%			
Severe Pain	31	2	6.5%			
Feelings of Suffocation	31	4	12.9%			

Note. Subscales of PHQ-D were used. Experiences at ICU were assessed with the PTSS-10. PHQ-D = Patient Health Questionnaire; PTSS-10 = Post Traumatic Stress Syndrome 10 Questionnaire; BAI = Beck's Anxiety Inventory; ICU = Intensive Care Unit.

Correlational Analysis. Table 50 shows the zero-order correlations between the planned serum biomarkers and the patient-file-derived values for CRP and LZ. There were strong correlations between the planned and patient-file-derived CRP presurgery values. Due to the incompleteness of study-based LZ values, no correlations could be made.

However, patient-file-based Leukocytes were possible to analyze. Preoperative LZ correlated with planned Preoperative CRP but not the patient-file-derived CRP values. Post-operative LZ peak correlated negatively with PCT at Visit 2 while at the ICU. LZ rise likewise correlated negatively with PCT at Visit 2. Expectedly, study-based CRP at

Visit 1 correlated positively with the preoperative CRP value derived from patient files. Likewise, study-based CRP levels at Visit 2 (while at ICU) correlated positively with the post-operative peak value of CRP derived from patient files.

However, preoperative values of CRP, whether study-based or patient-file derived, did *not* correlate with the peak or rise or Visit 2 values of CRP.

For completeness, a correlational analysis was conducted for the study-based biomarkers and cognitive tasks, as shown and Table 51with pair-wise case deletions. The usefulness of these study-based parameters is, however, very limited.

Better quality serum biomarker data from the patient files (i.e., presurgery, peak, and rise scores) were analyzed together with cognitive parameters, as shown in Table 52 and Table 53. Presurgery PCT levels were positively correlated with both simple and divided attention (TMT A, B) 6 months later but negatively correlated with cognitive speed (SDMT) measures and phonetic verbal fluency. In contrast, PCT at Visit 2 while at ICU post-surgery was only associated with the presurgery level of the same biomarker. NSE presurgery and postsurgery while at ICU correlated with CRP and each other but not with cognitive parameters. Post-surgery S100, but not presurgery S100, correlated negatively with verbal delayed recall (VLMT) 6 months later. As expected, presurgery IL-6 correlated positively with SIRS diagnosis and working memory (Digit Span backward) 6 months post-ICU. Post-surgery IL-6 did not correlate with any cognitive measure.

Table 50

Serum biomarker (patient-file based vs. study-based) correlation analysis

Biomarker	Pre-op CRP [b]	Peak CRP [b]	CRP Rise [b]	Pre-op LZ [b]	Peak LZ [b]	LZ Rise [b]	CRP V1 [a]	CRP V2 [a]	PCT V1 [a]	PCT V2 [a]	NSE V1 [a]	NSE V2 [a]	S100 V1 [a]	S100 V2 [a]	IL-6 V1 [a]
CRP peak [a]	.089	--													
rise [a]	.044	.958**	--												
LZ pre-op [a]	.033	-.067	-.090	--											
peak [a]	.030	-.043	-.054	.164	--										
rise [a]	.046	-.041	-.039	-.157	.682**	--									
CRP V1 [b]	.371*	-.096	-.160	.334*	.228	.101	--								
V2 [b]	-.043	.436**	.402*	-.167	-.291	-.172	.037	--							
PCT V1 [b]	-.114	-.175	-.186	.214	-.146	-.191	.017	.207	--						
V2 [b]	.010	.163	.177	-.124	-.324*	-.320*	-.148	.358*	.341	--					
NSE V1 [b]	-.065	-.255	-.191	-.016	.090	.143	.096	-.239	.210	.082	--				
V2 [b]	.077	.010	.024	-.171	.048	.148	-.252	-.453**	-.087	-.076	.245	--			
S100 V1 [b]	-.171	.186	.152	.090	.079	.000	-.125	.072	-.120	.111	-.380*	-.175	--		
V2 [b]	-.010	-.177	-.201	.039	.039	.024	.000	-.308	.138	-.029	.190	.361*	.138	--	
IL-6 V1 [b]	.089	.006	-.029	.152	.175	.187	.118	.032	.225	.088	.318	.072	-.088	.180	--
V2 [b]	.115	.029	-.033	.190	.029	-.033	.015	-.119	.325	.000	.201	.295	-.191	.429**	.360

Note. *N*= 31. Kendall's Tau Correlation. Listwise deletion of cases. CRP = C-Reactive Protein; PCT = Procalcitonin; NSE = Neuron-specific enolase; S100 = calcium-binding protein; IL-6 = Interleukin-6; LZ = Leukocytes. V1-2 = Visit 1-Visit 2.

[a] From patient files.

[b] Planned Biomarker Value.

** $p < .05$. ** $p < .01$.*

Table 51

Correlation analysis of cognitive and study-based biomarker parameters

Parameter	1	2	3	4	5	6	7	8	9	10	11	12
1. SIRS	-											
MMSE												
2. V1	.356	-										
3. V4	-.011	.595**	-									
4. V5	-.252	.144	.083	-								
VLMT												
5. Learning	-.286	.173	.165	.254	-							
6. Delayed Recall	-.291	.043	.154	.127	.739**	-						
Trail Making Test												
7. TMT-A	-.156	-.482**	-.293	-.172	-.342*	-.234	-					
8. TMT-B	.064	-.392*	-.454**	-.233	-.359*	-.316*	.363*	-				
9. SDMT	-.091	.299	.222	.342*	.568**	.469**	-.615**	-.492**	-			
Verbal Fluency												
10. Phonetic	-.037	.354*	.276	.302	.349*	.158	-.568**	-.221	.411**	-		
11. Semantic	-.019	.284	.143	.147	.239	.157	-.472**	-.164	.297	.399*	-	
WMS-R Digit Span												
12. Forward	-.280	.293	.136	.279	.294	.211	-.323*	-.460**	.367*	.186	.339*	-
13. Backward	-.390*	.182	.245	.357*	.305	.231	-.242	-.549**	.384*	.279	.281	

Table continues

Table 51

Correlation analysis of cognitive and study-based biomarker parameters (continued)

Parameter	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
CRP															
14. V1 [a]	.271	.215	-.045	-.076	-.107	-.050	-.126	-.019	.029	-.094	-.150	.005	-.101	-	
15. V2 [a]	-.108	.081	-.110	.267	.183	.096	.119	.012	-.141	-.132	-.061	.123	.000	.037	-
PCT															
										-					
16. V1 [a]	.048	-.114	-.226	-.216	-.268	-.200	.340*	.393*	-.403*	.524**	-.127	-.232	-.441*	.067	.112
17. V2 [a]	.324	.168	-.069	.059	-.160	-.204	.214	.106	-.317	-.180	-.294	-.136	-.273	.125	.287
NSE															
18. V1 [a]	.034	-.174	-.174	.000	-.215	-.050	.029	.242	-.010	-.159	-.085	-.312	-.268	.068	-.343
19. V2 [a]	.180	-.022	.233	.193	-.254	-.216	.036	-.141	.082	-.036	-.073	-.099	.104	-.258	-.427*
S100															
20. V1 [a]	-.265	-.064	.066	.006	.208	.085	-.021	-.144	.046	.291	.284	.153	.188	-.201	-.202
21. V2 [a]	.149	.098	.099	-.046	-.287	-.384*	-.073	.060	-.121	.155	-.006	.025	.087	-.084	-.356*
IL-6															
22. V1 [a]	.457*	.191	-.030	-.062	-.228	-.253	-.078	.067	-.005	-.153	-.107	-.185	-.352*	.247	-.216
23. V2 [a]	-.252	-.095	-.027	.015	-.160	-.156	.119	.117	-.059	-.312	-.171	-.012	-.026	-.037	-.076

Table continues

Table 51

Correlation analysis of cognitive and study-based biomarker parameters (continued)

Parameter	16	17	18	19	20	21	22
PCT							
17. V2 [a]	.450*	-					
NSE							
18. V1 [a]	.191	-.075	-				
19. V2 [a]	.000	.029	.358*	-			
S100							
20. V1 [a]	-.104	-.089	-.270	.056	-		
21. V2 [a]	.025	.054	.323	.452**	.233	-	
IL-6							
22. V1 [a]	.153	.072	.207	.248	-.083	.379*	-
23. V2 [a]	.257	.006	.433*	.251	-.186	.319	.424*

Note. N = 31. Kendall's Tau Correlation. Listwise deletion of cases. SIRS = Systemic Inflammatory Response Syndrome; MMSE = Mini-Mental State Examination; V1-V5 = Visit 1-Visit 5; VLMT = Verbal Learning and Memory Test; TMT = Trail Making Test; SDMT = Symbol Digit Modalities Test; WMS-R = Wechsler Memory Test-Revised; CRP = C-Reactive Protein; PCT = Procalcitonin; NSE = Neuron-specific enolase; S100 = calcium-binding protein; IL-6 = Interleukin-6.

[a] Planned Biomarker Value.

* $p < .05$. ** $p < .01$.SIRS Diagnosis was negatively correlated with the measure of working memory (digit span backward) and positively with presurgery IL-6. S100 post-surgery at Visit 2 was negatively correlated with delayed verbal recall (VLMT Trial 7). Presurgery PCT was positively correlated with both simple and divided attention (TMT A and B), which are negatively poled, as well as negatively correlated with cognitive speed (SDMT), phonetic verbal fluency as well as working memory (digit span backward).

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Table 52

Intercorrelations for MMSE, VLMT, and patient-file-based inflammatory biomarkers

Variable	*Zero-Order r*							
	SIRS	*MMSE V1*	*MMSE V4*	*MMSE V5*	*VLMT Learn.*	*VLMT Trial 6*	*VLMT Trial 7*	*VLMT Recog.*
CRP								
presurgery	-.010	.160	.025	-.080	-.106	-.174	-.102	.023
Peak	-.184	-.105	-.033	-.066	.048	.000	.029	.096
Rise	-.159	-.108	-.035	-.059	.048	.007	.036	.099
LZ								
presurgery	-.040	-.191	-.008	-.446**	-.148	-.098	-.069	-.032
Peak	.030	.151	.030	-.077	.198	.257*	.278*	.154
Rise	.090	.256	.025	.161	.266*	.295*	.283*	.101

Note. N = 31. Kendall's Tau Correlation. Listwise deletion of cases. CRP = C-Reactive Protein; LZ = Leukocytes; SIRS = Systemic Inflammatory Response Syndrome; MMSE = Mini-Mental State Examination; VLMT = Verbal Learning and Memory Test.

** p < .05. ** p < .01.*

There was a negative correlation between presurgery leukocyte level and MMSE score six months post-surgery. This relationship was not found for the presurgery MMSE or Month 4 MMSE performances. A positive association was found for the LZ peak level for the

interference and recall trials at the six-month visit A positive association was found between the LZ rise level and verbal learning, immediate recall after interference

(VLMT 6), and delayed recall (VLMT7) at Month 6. No associations were found for any CRP level and MMSE or VLMT.

Table 53

Intercorrelations visual memory, attention, processing speed, verbal fluency, working memory, and patient-file-based inflammatory biomarkers

	Zero-Order r									
Variable	VR 1	VR 2	VR Recog.	TMT-A	TMT-B	SDMT	Phon. VF	Seman. VF	DSF	DSB
CRP										
presurgery	-.112	-.071	.026	-.138	-.109	.026	-.060	.068	.111	.132
Peak	-.090	-.084	.062	.106	-.152	-.022	-.165	-.086	.002	.093
Rise	-.097	-.089	.074	.113	-.145	-.019	-.154	-.070	.005	.096
LZ										
presurgery	-.213	-.124	-.258	.024	.026	-.078	-.160	-.112	-.291*	-.340*
peak	-.078	.014	-.091	-.256*	-.227	.271*	.013	.209	.084	.063
Rise	.028	.082	.014	-.252*	-.221	.308*	.024	.272*	.175	.215

Note. N = 31. Kendall's Tau Correlation. Listwise deletion of cases. VR 1 = immediate Visual Recall; VR 2 = delayed Visual Recall; TMT = Trail Making Test; SDMT = Symbol Digit Modalities Test; VF = Verbal Fluency; DSF = Digit Span Forward; DSB = Digit Span Backward; CRP = C-reactive Protein; LZ = Leukocyte Count.

* $p < .05$.

As shown in Table 53, a negative relationship was found for both LZ Peak and Rise levels and the 6-month TMT A, and a positive relationship was found with the six-month SDMT. LZ presurgery levels were negatively correlated with both conditions of the digit span task at six months. At six months, a positive association was found with LZ rise and semantic but not phonetic verbal fluency.

Regression analyses

Logistic Regression Analyses of SIRS using age and preoperative MMSE level as regressors yielded strong evidence for age predicting SIRS by itself in Model 1, and age and preoperative MMSE together predicting SIRS in Model 2, as shown in Table 54.

Table 54

Results of Logistic Regression of SIRS with age and preoperative MMSE

	Coefficients						95% CI of *Exp (B)*		Model Change Statistics	
Regressor	*B*	*SE*	*Wald*	*df*	*Sig*	*Exp (B)*	*LL*	*UL*	-2 Log-Likelihood	Cox & Snell R-Quadrat
Model 1:										
Age	.066	.093	.506	1	.477	1.068	.890	1.282	22.654	.021*
Model 2:										
Age	.064	.094	.458	1	.499	1.066	.886	1.282	22.615	**.**022*
MMSE pre-op	-.095	.476	.040	1	.842	.910	.358	2.313		

Note. N = 31. SIRS = Systemic Inflammatory Response Syndrome, MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

Turning the causal direction around a hierarchical regression analysis of predictors of MMSE at Visit 1 using age and SIRS as regressors yielded no significant model, as shown in Table 55. Hence, preoperative cognitive ability appears to be a strong predictor of the occurrence of SIRS, but not the other way around.

Table 55

Hierarchical Regression results for SIRS and preoperative MMSE

	Coefficients					95% CI of *B*		Model Change Statistics		
Model	*B*	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	ΔR^2	*Adj.* R^2	*Sig.*
Model 1:										
Age	-.030	.027	-.211	-1.121	.272	-0.09	0.03	.044	.009	.272
Model 2:										
Age	-.030	.028	-.206	-1.066	.296	-0.09	0.03	.034	-.028	.855
SIRS	-.113	.608	-.036	-0.185	.855	-1.36	1.14			

Note. *N* = 31. SIRS = Systemic Inflammatory Response Syndrome, MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

Hierarchical linear regression analyses were chosen with pre-operative leukocytes, post-operative leukocyte peak, and the leukocyte rise as separate terms and entered as separate steps and, in that order, age as control variables and in parallel to the analyses in Study 2, as indicated. For each of the month 6 (Visit 5) cognitive parameters, the pre-operative MMSE and age were included as additional control variables in parallel to the analyses in Study 2. These same analyses were conducted for CRP levels likewise and are reported subsequently.

Hierarchical Regression Analyses of Leukocyte Levels

Hierarchical regression analyses of age, pre-operative, post-operative peak, and rise levels of leukocytes in a stepwise manner on preoperative MMSE score did not yield any predictive model, as shown in Table 56. The predictor LZ rise was excluded from the model in conjunction with age, presurgery and peak analysis, so that only 4 models were generated.

Table 56

Hierarchical Regression results for Leukocyte Count and preoperative MMSE

Model	Coefficients					95% CI of *B*		Model Change Statistics		
	B	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:										
Age	-.025	.025	-.184	-1.008	.322	-0.08	0.03	.034	.001	.322
Model 2:									-.018	
Age	-.023	.025	-.168	-0.905	.373	-0.08	0.03	.016		.502
LZ presurgery	-.085	.125	-.126	-0.680	.502	-0.34	0.17			
Model 3:										
Age	-.014	.025	-.102	-0.547	.589	-0.07	0.04	.072	.024	.149
LZ presurgery	-.141	.128	-.210	-1.104	.279	-0.40	0.12			
Peak	.076	.051	.286	1.487	.149	-0.03	0.18			
Model 4: Age	-.021	.029	-.151	-0.721	.477	-0.08	0.04	.010	-.002	.589
LZ presurgery	-.108	.143	-.161	-0.754	.458	-0.40	0.19			
Peak	-.089	.307	-.336	-0.291	.773	-0.72	0.54			
Rise	.022	.040	.611	0.547	.589	-0.06	0.11			
Presurgery x Rise	-.021	.029	-.151	-0.721	.477	-0.08	0.04			

Note. N = 31. SIRS = Systemic Inflammatory Response Syndrome, MMSE = Mini-Mental State Examination, LZ = Leukocyte; CI = confidence interval; LL = lower limit; UL = upper limit.

As shown in Table 57 the first model, which included only preoperative MMSE, and the third model, which included MMSE, age, and preoperative Leukocytes together explained

Table 57

Hierarchical Regression results for Leukocyte Count and 6-month MMSE

	Coefficients					95% CI of *B*		Model Change Statistics		
	B	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:										
Presurgery										
MMSE	.417	.167	.420	2.491	.019*	.075	.760	.176	.148	.019*
Model 2:										
Presurgery										
MMSE	.405	.173	.408	2.342	.027*	.051	.759	.004	.122	.705
Age	-.009	.024	-.066	-0.382	.705	-.057	.039			
Model 3:										
Presurgery										
MMSE	.351	.158	.353	2.225	.035*	.027	.675	.173	.282	.012*
Age	-.003	.021	-.023	-0.146	.885	-.047	.041			
LZ presurgery	-.282	.105	-.423	-2.689	.012*	-.498	-.067			
Model 4:										
Presurgery										
MMSE	.390	.165	.392	2.363	.026*	.051	.728	.018	.274	.403
Age	-.007	.022	-.050	-0.310	.759	-.052	.038			
LZ presurgery	-.250	.112	-.375	-2.233	.034*	-.481	-.020			
Peak	-.039	.046	-.147	-0.851	.403	-.132	.055			
Model 5:										
Presurgery										
MMSE	.399	.168	.401	2.372	.026*	.052	.745	.007	.378	.607
Age	-.001	.025	-.009	-0.050	.960	-.052	.050			
LZ presurgery	-.276	.124	-.414	-2.225	.035*	-.532	-.021			
Peak	.096	.263	.364	0.365	.718	-.446	.639			
Presurgery x Rise	-.018	.035	-.505	-0.521	.607	-.090	.054			

Note. *N* = 31. SIRS = Systemic Inflammatory Response Syndrome; MMSE = Mini-Mental State Examination; LZ = Leukocyte; ; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

more than 28.2% of the variance of the 6-month postoperative MMSE level, with the inclusion of preoperative leukocyte level increasing explanatory power by more than 17%. Neither

rise level nor peak level of LZ provided greater explanatory power. In addition, the interaction term preoperative and rise added no more explanatory power.

Hierarchical Regression analyses using the same modeling of leukocyte levels, including the control variables preoperative MMSE and age, did not yield any meaningful models for verbal learning (VLMT Sum of 1-5 Trials), short-delayed verbal recall (VLMT 6), long-delayed verbal recall (VLMT 7), nor recognition of the VLMT word list which included any leukocyte level.

Analyses of TMT A, TMT B, and SDMT yielded meaningful models using preoperative MMSE and age only, but not when any leukocyte parameter was included in the modeling. In the same vein, no leukocyte regressor added explanatory power to regression models of phonetic or semantic verbal fluency beyond age and preoperative MMSE (Appendix E).

Likewise, no leukocyte regressor added any additional explanatory power to variance in the WMS-4 digit span forward task beyond that of preoperative MMSE (Model 1 preoperative MMSE Adjusted $R^2 = .226$, $p = .004$). For space reasons, these models are included in the appendix (Appendix E).

Preoperative leukocyte level was a meaningful regressor for the WMS-4 digit span backward task, in addition to preoperative MMSE and age, as is shown in Table 58. This model (Model 3) explained 34.8% of the variance of Digit Span backward, with more than 17% of explanatory power due to the inclusion of preoperative Leukocyte level as a regressor.

Further analyses of the WMS-IV Visual reproduction tasks yielded no meaningful models for the immediate recall task. There was a meaningful model for the long-delayed task using the preoperative MMSE level only. No meaningful model fit the WMS-IV Visual Recognition task (Appendix E).

Table 58

Hierarchical Regression results for Leukocyte Count and TMT-A

	Coefficients					95% CI of *B*		Model Change Statistics		
	B	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:										
Presurgery										
MMSE	.698	.303	.393	2.305	.029*	.079	1.317	.155	.126	.029*
Model 2:										
Presurgery										
MMSE	.698	.303	.393	2.305	.029*	.079	1.317	.087	.188	.083
Age	-.073	.040	-.301	-1.798	.083	-.155	.010			
Model 3:										
Presurgery										
MMSE	.504	.268	.284	1.879	.071	-.046	1.054	.171	.348	.009*
Age	-.062	.036	-.258	-1.710	.099	-.137	.012			
LZ presurgery	-.501	.179	-.420	-2.804	.009*	-.867	-.134			
Model 4:										
Presurgery										
MMSE	.541	.283	.305	1.910	.067	-.041	1.122	.005	.329	.640
Age	-.066	.038	-.272	-1.745	.093	-.143	.012			
LZ presurgery	-.470	.192	-.394	-2.444	.022*	-.866	-.075			
Peak	-.037	.078	-.079	-.473	.640	-.198	.124			
Model 5:										
Presurgery										
MMSE	.529	.289	.298	1.827	.080	-.067	1.125	.003	.306	.704
Age	-.073	.042	-.302	-1.714	.099	-.160	.015			
LZ presurgery	-.437	.214	-.367	-2.045	.052	-.878	.003			
Peak	-.209	.453	-.443	-.460	.649	-1.142	.725			
Presurgery x Rise	.023	.060	.359	.385	.704	-.101	.147			

Note. *N* = 31. Intercept Model 1 = -14.776, Intercept Model 3 = -1.516. TMT = Trail Making Test. SIRS = Systemic Inflammatory Response Syndrome; MMSE = Mini-

Mental State Examination; LZ = Leukocyte; ; CI = confidence interval; LL = lower limit; UL = upper limit.

** $p < .05$.*

Hierarchical Regression Analyses of C-Reactive Protein Levels

The results of hierarchical regression analyses using age, pre-operative MMSE and CRP, post-operative CRP, and rise levels of CRP with all cognitive parameters as dependent variables were conducted similarly for leukocytes. Global cognition as measured by MMSE was not predicted by any CRP level nor age either at Visit 1 prior to surgery or six months after ICU.

Verbal learning was predicted by age only (verbal learning: Adj. $R^2 = 13.1\%$, $p = .026$), but not by any CRP parameter. Short and long-delayed verbal memory and recognition yielded no meaningful models based on age or CRP variables (please see Data in Appendix E).

Simple attention (TMT-A) was predicted by preoperative MMSE and age (Model 2 Adj. $R^2 = 51.1\%$, $p = .020$), but not by any CRP regressor. Divided attention (TMT-B) was predicted by preoperative MMSE and age (Model 2: Adj. $R^2 = 41.9\%$, $p = .019$), but not by any CRP parameter. Cognitive Processing Speed (SDMT) was also predicted by preoperative MMSE and age and not by any CRP parameters (Model 2: Adj. $R^2 = 10.8\%$, $p = .034$).

Digit Span Forward could only be explained by preoperative MMSE (Model 1: Adj. $R^2 = 25.2\%$, $p = .004$) and not by any other regressor, including age.

Digit Span Backward showed comparable results, as in Table 59, with preoperative MMSE (Model 1) explaining 15.5% of the variance. There, too, the addition of age and preoperative CRP level did not increase explanatory power. However, Model 4, which added the regressor CRP Rise came close to representing a meaningful model ($p = .059$).

Table 59

Hierarchical Regression results for CRP and Digit Span Backward

	Coefficients					95% CI of *B*		Model Change Statistics		
	B	*B*	*SE*	*T*	*Sig*	*LL*	*UL*	ΔR^2	*Adj.* R^2	*Sig.*
Model 1:										
MMSE V1	.698	.303	.393	2.305	.029*	0.08	1.32	.126	.155	.029*
Model 2:										
MMSE V1	.600	.297	.338	2.020	.053	-0.01	1.21	.188	.087	.083
Age	-.073	.040	-.301	-1.798	.083	-0.16	0.01			
Model 3:										
MMSE V1	.677	.305	.382	2.218	.035*	0.05	1.30	.191	.030	.301
Age	-.072	.040	-.299	-1.792	.084	-0.16	0.01			
CRP pre-op	-.114	.108	-.178	-1.055	.301	-0.34	0.11			
Model 4:										
MMSE V1	.800	.297	.451	2.699	.012*	0.80	0.29	.270	.095	.059
Age	-.053	.040	-.218	-1.326	.196	-0.05	0.04			
CRP pre-op	-.123	.103	-.194	-1.203	.240	-0.12	0.01			
rise	.012	.006	.323	1.974	.059	0.01	0.01			
Model 5:										
MMSE V1	.761	.298	.429	2.554	.017*	0.15	1.38	.273	.027	.297
Age	-.050	.040	-.206	-1.254	.222	-0.13	0.03			
CRP pre-op	-.324	.214	-.508	-1.511	.143	-0.77	0.12			
rise	.006	.008	.177	0.830	.414	-0.01	0.02			
CRP pre-op x rise	.002	.002	.390	1.064	.297	-0.00	0.01			

Note. N = 31. Intercept Model 1 = -14.776; Intercept Model 4 = -15.750. CRP = C-reactive Protein; MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

Neither the phonetic verbal nor semantic verbal fluency tasks were predicted in hierarchical regression analyses using either preoperative MMSE level, age, or CRP levels (Table 60, also please see Data in Appendix E).

No model could explain immediate visual memory (Visual Reproduction 1). Delayed visual memory (Visual Reproduction 2) was explained by preoperative MMSE only (Model 1: Adj. R^2 = 13.9 %, p = .024). However, the third Model, which included preoperative MMSE, age, and preoperative CRP, came close to being a meaningful model: (Model 3: Adj. R^2 = 18.4 %, p = .073). For the full data output, please see Appendix E.

The regression analyses of the visual memory recognition task with preoperative MMSE and age as regressors did not yield significant models. However, the further inclusion of preoperative CRP levels did yield a meaningful model, in which preoperative CRP had the largest Beta-weight compared to preoperative MMSE or age, as shown in Table 60. This model (Model 3) could account for 23.5 % of the variance of the visual memory recognition task.

Table 60

Hierarchical regression results of CRP and Visual Recognition

	Coefficients					95% CI of *B*		Model Change Statistics		
	B	*β*	*SE*	*T*	*Sig*	*LL*	*UL*	Δ R^2	*Adj.* R^2	*Sig.*
Model 1:										
MMSE V1	.033	.337	.019	0.097	.923	-0.66	0.72	-.037	.000	.923
Model 2:										
MMSE V1	.004	.345	.002	0.010	.992	-0.71	0.71	-.062	.013	.561
Age	-.023	.039	-.116	-0.589	.561	-0.10	0.06			
Model 3:										
MMSE V1	.173	.313	.099	0.554	.584	-0.47	0.82	.158	.235	.010*
Age	-.022	.035	-.110	-0.628	.535	-0.09	0.05			
CRP pre-op	-.260	.093	-.494	-2.796	.010*	-0.45	-0.07			
Model 4:										
MMSE V1	.200	.322	.114	0.620	.541	-0.47	0.87	.132	.007	.633
Age	-.017	.037	-.088	-0.478	.637	-0.09	0.06			
CRP pre-op	-.262	.095	-.498	-2.771	.011*	-0.46	-0.07			
rise	.003	.005	.089	0.484	.633	-0.01	0.01			
Model 5:										
MMSE V1	.178	.326	.102	0.548	.589	-0.50	0.85	.120	.021	.421
Age	-.015	.037	-.078	-0.419	.679	-0.09	0.06			
CRP pre-op	-.406	.199	-.771	-2.036	.053	-0.82	0.01			
rise	-.001	.007	-.038	-0.159	.875	-0.02	0.01			
CRP pre-op x rise	.001	.001	.339	0.820	.421	-0.00	0.00			

Note. N = 31. Intercept Model 3 = 4.729. CRP = C-reactive Protein; MMSE = Mini-Mental State Examination; CI = confidence interval; LL = lower limit; UL = upper limit.

* $p < .05$.

MRMM analysis

In order to answer the question as to whether cognitive changes over time are related to systemic inflammation, a series of MRMM analyses were conducted using the three MMSE assessments. This analysis method could not be applied to this study's full set of cognitive measures since they were only assessed once.

Diagnosis of SIRS

The MMRM analysis included SIRS, time, a SIRS*time interaction term with sex, and age as covariates, with the repeated dependent variable being MMSE at Visit 1 (pre-surgery), Visit 4 (3-4 months post-surgery), and Visit 5 (6 months post-surgery) in Table 61. All terms were defined as fixed effects. This analysis yielded no main effect of SIRS diagnosis (p = .655), no main time effect (p =.479) nor of the interaction term SIRS*time (p = .672). There was a fixed effect of sex (*p* = .004) and age (*p* =.009).

Hence, no decline over time occurred in association with SIRS diagnosis using MMSE as a proxy for global cognition over the six months of study.

Table 61

Summary of fixed effects of MMRM of SIRS as a predictor of MMSE

						95% CI	
Parameters	*Estimate*	*Std. Error*	*df*	*t*	*Sig.*	*LL*	*UL*
No SIRS	.519	.548	87.00	0.947	.346	-0.57	1.61
age	-.038	.014	87	-2.674	.009**	-0.07	-0.01
Sex	.740	.249	87.00	2.969	.004**	0.25	1.24

Note. N = 31. These are fixed parameter estimates for the main effect of the SIRS, along with age and sex. Intercept = 30.126. SIRS = Systemic Inflammatory Response Syndrome; MMSE = Mini-Mental State Examination.; CI = confidence interval; LL = lower limit; UL = upper limit.

** p < .05.*

The general level of cognition prior to surgery among those with SIRS was equivalent to those who did not develop SIRS. At the 6-month mark, there was only around half a point difference in MMSE out of 30 points.

C-Reactive Protein

The results of the Type III tests of fixed effects for each of the three MMRM analyses using CRP presurgery, rise or peak values, including the interaction with time, denoted "change over time," are given in Table 62.

The presurgery CRP (Model 1) showed several main effects: CRP, time, and a notable change over time. Sex *(p* = .007) but not age *(p* = .05) had main effects. CRP Rise also had a main effect, as did time itself, and change over time (Model 2). Age, but not sex, also had main effects (data not shown). Peak CRP had a main effect, as did time itself, and change over time (Model 3). Age ($p > .001$), but not sex had a main effect in Model 3. Due to the finite number of data points in this small sample, more complex models analyzed in Studies 1 and 2 using interaction terms presurgery*rise level were impossible to calculate.

Table 62

Summary of fixed effects of MMRM of CRP predictors of MMSE

MMRM Model	Main Effect	Change over Time
	Sig.	*Sig.*
1. Presurgery	.001**	.010*
2. Rise	<.001***	<.001***
3. Peak	<.001***	<.001***

Note. N = 31. The p-values for the main effect as estimated by sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 3 MMSE assessments. These analyses include age and sex as fixed effects. Rise: Peak level post-surgery minus presurgery level. CRP = C-reactive Protein; MMSE = Mini-Mental Status Examination.

Leukocyte Count

The results of the Type III tests of fixed effects for each of the five MMRM analyses using Leukocyte count presurgery, rise, or peak values are given in Table 63, including the interaction with time, denoted "change over time." Due to the limited number of data points in this small sample, the presurgery LZ (Model 1) could not be calculated. In addition, some main effects could not be reported, and more complex models analyzed in Studies 1 and 2 were impossible to calculate.

LZ Rise (Model 2) showed no main effect, neither of time nor change over time. Neither sex nor age had main effects. Peak LZ likewise had no main effect, time itself, or change over time (Model 3). A main effect of age or sex was also not found.

Table 63

Summary of fixed effects of MMRM Analyses of Leukocyte Count predictors of MMSE

MMRM Model	Main Effect	Change over Time
	Sig.	*Sig.*
Presurgery	x	x
Rise	.163	.585
Peak	.233	x

Note. N = 31. These are the p-values for the main effect as estimated by sum of squares type 3 of the proinflammatory marker level and interaction with time of proinflammatory marker level and time over the 3 MMSE assessments. These analyses include age and sex as fixed effects. Rise: Peak level post-surgery minus presurgery level. MMSE = Mini-Mental State Examination.

Discussion

Hypothesis 1: Are higher levels of chronic inflammation associated with indicators of acute inflammation? Intracytokinic correlations varied considerably across biomarkers. Study-based inflammatory biomarkers indicated that pre- and post-operative levels were highly correlated for PCT and NSE. No intra-cytokinic correlation was found for study-based CRP or S100. The patient-file-derived CRP and Leukocyte values yielded no intra-cytokinic correlations. Strong correlations were found between the study-based and patient-file-derived CRP presurgery values and those of the presurgery LZ value.

A cross-sectional comparison of markers showed that pre-operative IL-6 level strongly correlated with the clinical diagnosis of systemic inflammatory response SIRS ($\rho = .457$, $p < .05$). IL-6 was the only biomarker to do so in this study.

The pre-operative CRP level did not correlate with any other pre-operative inflammatory marker studied. In contrast, the Post-operative CRP level strongly negatively correlated with the postsurgery NSE and post-surgery S100 levels. Neither the pre- nor the postsurgery PCT levels were associated with any inflammatory marker other than one another. The presurgery NSE level positively correlated with post-surgery IL-6 and itself. The presurgery S100 level did not correlate with any other marker. The post-surgery S100 level strongly correlated with the postsurgery NSE level.

Hypothesis 2: Are chronic and acute inflammation negatively associated with cognitive performance over time? This hypothesis found some support among a few markers of chronic inflammation in the BonSEP correlational analysis using serum biomarkers planned for analysis within the larger study, but the direction of association varied between serum Biomarkers.

A positive rather than negative association was found for pre-operative IL-6 level and digit span backward six months later. Not discovering any associations with post-operative IL-6 levels in this study likely had to do with missing data and so limited power. Thus, it may be that higher chronic IL-6 levels indicate *greater* cognitive health.

The *pre-operative* level of Procalcitonin showed varied valences of association with different cognitive Tasks. PCT had strong negative association with cognitive processing SDMT. The strong positive associations with both conditions of the Trail Making Task yield a consistent result since TMT tasks were reversely poled. All three tasks employ speed and visual-spatial processing abilities. Nevertheless, pre-operative PCT showed strong positive associations with phonetic verbal fluency and the digit span backward task six months later. These tasks are highly language-oriented executive tasks.

Turning to acute biomarkers of inflammation: the acute systemic clinical diagnosis of SIRS was strongly negatively correlated with the 6-month digit span backward task in Kendall's Tau correlational analysis. The postsurgery S100 level was strongly negatively associated with delayed verbal recall performance six months later. No other planned comparison showed an association with general cognitive performance (MMSE) prior to surgery, at the 3-4 month or 6-month visit.

The secondary analyses using CRP levels from patient files, CRP levels (presurgery, peak, and rise) yielded no relationship to any cognitive parameter at any time point. Since there was a clear, dynamic change in CRP level over the hospital stay in this

study, on the one hand, and several reports of negative associations between chronic CRP levels and cognition

for several other cohorts, this was surprising (Dlugaj et al., 2012; Tegeler et al., 2016; Weinstein et al., 2017). However, high levels of CRP have previously also been found among those with normal cognitive abilities (Buchman & Bennett, 2012).

In contrast, the post hoc examination of patient file-based leukocytes showed that the presurgery level of leukocytes was strongly negatively associated with general cognition (MMSE) 6 months later. Presurgery leukocyte level was also moderately and strongly negatively correlated to digit span forwards and backward, respectively. This marker did not have any association with verbal learning or memory. Thus, a higher presurgery leukocyte count may be specific to loss of ventral frontal lobe integrity, which could affect general cognition but not learning and memory.

These presurgery leukocyte findings are consistent with the hypothesis that chronic higher levels of leukocytes may be detrimental to working memory or processing speed. Higher leukocyte counts have been associated with worse cognitive performance, for example, among aging North Americans (Kao et al., 2011a; Li et al., 2021).

In contrast, the peak level of leukocytes after surgery was moderately *positively* correlated with short-delayed long-delayed recall trials in the VLMT. In addition, postsurgery peak leukocyte level was moderately negatively correlated with TMT A and positively correlated with SDMT.

Furthermore, the related, but separately examined, leukocyte rise level *positively* correlated with the learning trials, short- and long-delayed verbal recall trials of the VLMT. Hence, the rise levels may be a good indicator of a working immune response, which later is associated with *better* verbal learning and memory performance. LZ Rise

level was negatively correlated with simple attention (TMT A) and positively correlated with general cognitive processing (SDMT) and semantic verbal fluency.

The findings are inconsistent with reports of aged US-Americans in which higher leukocyte counts were negatively associated with cognitive performance on cognitive speed tasks such as letter digit substitution tests (Kao et al., 2011a; Li et al., 2021). It has been speculated that this would also hold for leukocyte count in Post-operative patients (Y. Liu & Yin, 2018), but the data in Study 3 did not support this. In sum, this is the first study to demonstrate the dynamics of leukocyte count post-surgery and *positive* associations with later cognition among post-operative patients.

Hypothesis 3: Do chronic and acute systemic inflammation negatively impact the trajectory of cognitive performance over time? The results of repeated mixed model calculations in Study 3 indicated that SIRS did not have a main effect on MMSE over time. This finding contrasted starkly with the CRP values derived from patient files: there was a main effect and a change over time for presurgery, peak, and rise values of CRP. Unfortunately, too few data points made it impossible to include interaction terms in the MMRM model. Too few data points partially hindered the analysis of leukocytes using MMRM analyses of leukocytes. Hence, the effect of presurgery leukocyte and rise levels remain unclarified. There was no evidence of an effect of peak leukocyte levels on MMSE.

Hypothesis 4: Is there an interaction between chronic and acute inflammation on cognitive performance? In this cohort, no interaction between chronic and acute inflammation affected cognitive performance in hierarchical regression analyses using CRP or Leukocyte counts.

OVERALL DISCUSSION

The thesis aimed to characterize the associations between chronic and acute levels of inflammation on cognitive abilities in three cohorts of major surgery patients in the intensive care unit. This novel approach to the analysis used two innovations compared to previous studies on cardiac surgery patients. The first was the inclusion of the dynamics of the acute inflammatory response to surgical procedures, i.e., the natural rise in inflammatory biomarker levels, as a potentially crucial factor in predicting later cognitive ability. A second novel methodology compared presurgery and acute inflammation as separate and potentially equal contributors to cognitive performance. The literature on inflammatory biomarkers and cognitive performance among thorax surgery patients is quite small. Most studies that have assessed both types of data have not compared them. So far, none has compared the dynamics of presurgery and post-operative rise parameters and their associations with cognition. Of the few studies that have compared cognitive data and inflammatory markers, they only looked at very short-term cognition (i.e., assessed the immediate postoperative period up to no more than a week). In addition, there was a broad spectrum of inflammatory biomarkers used across previous studies. Hence, there is still a lack of consensus in the research community about which inflammatory markers may be most important in association with cognitive processes. In this thesis, three common markers of inflammatory states, i.e., C-Reactive Protein, Leukocyte count, and the clinical syndrome of Systemic Inflammatory Response, were consistently compared across three cohorts. This kind of systematic assessment enables broader conclusions about the relationships of these markers to cognition. A synthesis of all main results in this thesis across studies is given in five tables in Appendix A.

The first important finding in this thesis was the attempt to assess the dynamic shift in biomarker levels after surgical treatment (Appendix A, Table 1). In all three studies,

CRP was abnormally high in 40-60% of patients prior to surgery, which shifted to between 90-97% after surgery. Also, leukocyte levels were very low (abnormal in only 3-7%) across cohorts prior to surgery. The dynamics after surgery differed across the studies, however. The leukocyte count was abnormally high in Studies 2 and 3 after surgery (70% and 97%, respectively). However, in Study 1, leukocyte levels normalized after heart surgery, with all patients lying within the normal post-surgery peak levels.

Beyond the commonality of CRP, Leukocyte Count, and SIRS, the biomarker panels did vary considerably across the three studies. This broad range of biomarkers results from a lack of consensus about the most meaningful inflammatory biomarkers. However, the original foci of the studies were not to investigate chronic and acute inflammation on cognition. Thus, Study 1 was the most comprehensive, employing a total of 6 biomarkers that were consistently assessed before and after surgery. Study 1 was thus able to encapsulate the dynamic shifts after surgery in addition to the serum biomarkers PCT, IL-6, and IL-8. Study 2 employed only CRP and Leukocytes since the focus of that study was largely on critical care outcomes and not on inflammatory markers. The biomarker panel in Study 3 was initially very extensive, with a separate set of 7 biomarkers. This study was ambitious in its planning, yet too few data points were consistently assessed in the perioperative period after surgery to draw any conclusions between PCT, IL-6, NSE, and S100. Thus, a similar approach to Study 3 was taken as in Study 2 by modeling CRP and leukocyte counts, which included dynamic shifts in biomarker level and SIRS diagnosis.

A second major finding was that of relatively stable cognitive functioning prior to surgery and afterward in all three studies (Appendix A, Tables 1). Hence, the total RBANS score in Study 1 was close to two standard deviations below the age norm prior to surgery at the 12-month study assessment. This pattern was similar in Study 2, based

on MMSE presurgery and the telephone version of MMSE 6 months post-surgery (both MMSE index scores were 90%). Moreover, in Study 3, the MMSE Score presurgery and at six months post-surgery were also consistently high, with an average of 29 points. Similarly, the average score of most parameters at the comprehensive 6-month follow-up visit in Study 3 was around 1.5 standard deviations below that of age- sex, and educational level norm values.

Deviating from this general pattern was a cognitive performance in the subgroup of patients in Study 2 who were also administered the RBANS. Those patients, as a group, showed considerable *improvement* between low presurgery RBANS scores (approx. 85/100 standard value points) compared to the six months post-surgery scores (approx. 100/100 standard value points), i.e., by 1.5 standard deviations. By the 6-month assessment, this subgroup performed well within the normal range for their age.

This deviation in the overall pattern of results in the subgroup of Study 2 raises critical questions: 1) what contributed to the improvement in scores and 2) what contributed to lower scores prior to surgery in that group. Factors such as psychological burden (worry, anxiety) in advance of major heart surgery could have contributed to worse performance prior to surgery.

This, however, would also hold for the surgery patients in Studies 1 and 2. Another alternative may be that the types of heart surgery in Study 2 directly lead to improvement in cognitive ability. However, the mortality rate may explain the outcome in Study 2. This subset of patients who received additional testing may have been those with better health to begin with prior to surgery. Support for this is that the mortality rate for those who received additional testing was 0%. However, mortality rates were highest in Study 2 (at 32%) compared to only 4% in Study 1, with no mortality cases in Study 3. In addition, there were considerable differences in the average duration of surgery across studies,

which may account for differences in cognitive results. The shortest surgery duration was the minimally invasive TAVI surgery in Study 1, the next being CABG and heart valve replacement patients in Study 2, and the longest surgeries occurring in Study 3 patients, the majority of whom had had CABG or heart valve implants, but also, in one case, major stomach surgery.

The number of patients who experienced even one day of delirium was similar in Studies 1 and 2 (around 30%), but none experienced delirium in Study 3. However, even these assessments were not very dependable as delirium was difficult to assess accurately or consistently in any of the studies.

Further differences were also found in the comorbidities of patients across the studies. Thus, the co-occurrence of diabetes mellitus type 2 varied greatly between around 30% in Studies 1 and 2 and none in Study 3. The hospital stay was, on average longest among patients of Studies 1 and 2 (each around 18 days) compared to around 13 days in Study 3. The average preoperative MMSE score was lowest in Study 1 (25 Points) compared to Study 2 (27 points) and Study 3 (29 points).

In addition, there were large differences in the sample sizes ranging from 125 in Study 1, 224 in Study 2 main analysis, 46 in Study 2 subanalysis, and only 31 in Study 3. There were also differences in gender distribution: the number of men as a percentage of the study population varied from 53% in Study 1 to 66% in Study 2 to 71% in Study 3. The ages of the patient populations varied, with the oldest in Study 1 at, on average, 80 years of age, 70 years of age in Study 2, and the youngest average age group in Study 3 at 65 years.

The studies also differed in the length and breadth of the neuropsychological tests used (MMSE, RBANS in Studies 1 and 2 and the most complex and comprehensive in Study 3). There were some differences in the percentage of patients who had a SIRS

diagnosis after surgery, with around a third (33-34%) in Studies 1 and 2 compared to a mere 13% in Study 3.

Despite these differences, or more precisely, *because* of these differences, consistent findings across studies would yield meaningful and valid results. In this respect, due to differences in study design across the three studies, distinct kinds of analysis ranged from correlational analysis and hierarchical regression to MMRM. The main results at each level of analysis, starting with the clinical syndrome SIRS and for each biomarker studied, will be outlined next.

Systemic Inflammatory Response Syndrome

Although SIRS has been associated with higher mortality rates (Schwietz et al., 2015), the current literature on thorax surgery patients, which includes biomarkers of inflammation and cognitive ability, does not include any analysis of systemic inflammatory response syndrome, also known as SIRS, making this approach novel to this thesis.

A bird's eye view of the findings in this thesis showed a robust negative correlative association between presurgery MMSE and SIRS diagnosis in Study 1 only, but not in Studies 2 or 3 (Appendix A, Table 2). No zero-order correlation was found between long-term postoperative cognition measured by either MMSE or RBANS and the clinical diagnosis of SIRS in any of the three studies (Appendix A, Table 3). This likely reflects the comparatively small number of SIRS patients and the small sample sizes in Studies 2 and 3.

The use of hierarchical regression analysis did not show a relationship between SIRS and cognitive ability in either Study 2 analyses of the full data set of 224 Patients who also had an MMSE or in the smaller subset of 46 patients who also had more comprehensive testing using the RBANS (Appendix A, Table 4). Likewise, SIRS did not

show any relationship to MMSE at Months 3-4 after surgery, not at six months post-surgery in Study 3. Indeed, in Study 3, SIRS did not yield any explanatory power for any cognitive parameter measured six months after surgery.

However, the use of multilevel modeling with repeated measures (MMRM) did show a main effect of SIRS on general cognitive ability as assessed by RBANS in Study 1. There was no interaction with time; hence, no difference in the trajectory of cognitive performance over time. Although this finding could not be replicated in the subset of patients in Study 2 or the full data set of Study 3, this is likely due to their much smaller sample sizes (Appendix A, Table 5).

Hence, the results of Study 1 warrant further consideration. Support for the idea that the actual relationship between SIRS and cognition in Study 1 may be due to a third underlying variable is the fact that, on average, patients in Study 1 had comparatively low cognitive ability prior to surgery (around one and a half standard deviations below the norm), which continued throughout the 12-month follow-up. This may be due to a compromised immune system before surgery, which is also associated with lower cognitive performance. This idea would be in line with similar findings reported in other patient populations who also experience SIRS, such as patients experiencing sepsis-associated encephalopathy, an acute inflammatory condition closely associated with SIRS, and, most recently, in a study of COVID-19 patients who also experience Sepsis or SIRS (Annane & Sharshar, 2015; Golzari & Mahmoodpoor, 2014; Stallmach et al., 2022). These findings are also in line with longitudinal population studies of patients with pneumonia with lower cognitive ability and a higher risk of hospitalization due to pneumonia, an acute inflammatory disease of the lungs (Jo et al., 2017; Shah et al., 2013b).

Turning the predictive model around to examine whether preoperative cognitive ability could predict the presence of SIRS after heart surgery was conducted using logistic regression analysis with age, preoperative MMSE, and preoperative RBANS score in separate steps. The final model included both age and preoperative MMSE with a considerably larger regression coefficient (β = -.234, $p < .001$) for MMSE than for age (β = -0.64, p = .046). Premorbid RBANS was not included in the final model (Appendix C). This analysis was replicated for Studies 2 and 3 but yielded no explanatory power of preoperative MMSE for the occurrence of SIRS (Appendix C).

C-Reactive Protein

The presurgical level of serum-based CRP was abnormally high in around half of the patients in each of the three studies before surgery. Despite this, presurgery cognitive performance (based on the MMSE) had no zero-order correlation with C-reactive protein in any of the three studies. The use of hierarchical regression in Studies 2 and 3 showed no relationship between preoperative MMSE and any CRP values at any time. These findings are generally supported by Poole et al. (2016), in which a presurgery cognitive score (MoCA) 30 days before surgery was unrelated to perioperative plasma-based CRP level.

At a more granular level of cognitive function post-surgery, hierarchical regression analysis did show that preoperative CRP level could help predict worse performance on the visual memory recognition task 6 months post-surgery in Study 3.

Further, using MMRM analyses of CRP parameters yielded varying results across studies. For Study 1, only *peak* CRP was associated with repeated RBANS total score without being associated with changes in longitudinal trajectory over time. In Study 2, *no* CRP measure predicted repeated MMSE. In Study 3, however, *each CRP-related parameter* was a good predictor of repeated MMSE performance. This last finding was

more surprising given that this study had the smallest sample size. Hence only in study 3 was a difference in the trajectory of cognitive ability over time attributable to serum-CRP levels, both the presurgery, peak, and rise levels of serum-CRP.

These findings were in line with Ramlawi et al. (2006), which found higher CRP levels in the five days post-surgery among those with neurocognitive decline defined at baseline compared to those without neurocognitive decline, on a magnitude of 38.01 (11.4) vs. 16.49 (3.5) mg/L. The duration of the follow-up in Ramlawi et al. study was a mere 4 to 5 days post-surgery. One study of 108 women undergoing cardiac surgery and 58 female controls who were not hospitalized found that pre-operative CRP was higher in those undergoing cardiac surgery compared to controls but was not predictive of pre-operative cognitive ability in multivariate logistic regression analysis controlling for age, education, type 2 diabetes, and history of myocardial infarction (Hogue et al., 2006).

In the review of comparable research synthesized at the outset of this thesis, C-reactive protein was assessed in six studies, but only three also assessed cognition in a directly comparable nature. Despite Christiansen et al. (2016), Matthew et al. (2009), and Skrabal et al. (2006) all evaluated CRP along with broad cognitive test batteries, these studies provided no analysis of potential associations between cognition and CRP.

Further afield, large-scale epidemiological studies comparing cognitive performance and CRP in non-hospitalized population measures show mixed results.

A large-scale study of over twenty-thousand US Americans (the REGARDS Study) found that plasma-CRP was associated with worse *memory and verbal fluency at* a baseline visit but did not have ramifications for the trajectory of cognitive decline over their 12-year follow-up (Rentería et al., 2020). This study used latent growth curve models, including stratifications based on geography and race in adults 45 years and older

employed the CERAD test battery every two years. The findings would partially support Study 1 findings but not those of Study 3.

Further, Stevenson et al. (2020) evaluated serum CRP and cognition in an older large-scale British cohort (approximately one thousand people born in 1936 with a follow-up time of around 11 years) as well as in a smaller, younger, cross-sectional cohort (approximately 400 Scottish participants between 18-65 years of age). Serum-CRP was negatively associated with cognitive performance at baseline data in the older cohort, yet after adjusted latent class models to account for several potentially confounding variables such as BMI, smoking, alcohol use, and deprivation experiences, this relationship disappeared.

The authors also compared three CRP score types, which yielded differing results. The longitudinal cohort study found that serum-based CRP and genetic CRP scores had no relationship to the trajectory of cognitive performance during follow-up. However, they did find an "epigenetic CRP score" (a DNA methylation-based CRP score) to be negatively associated with cognitive performance even after adjusting for confounding effects. A large-scale study of more than 3,500 US Americans (US Health and Retirement Study) likewise found that elevated serum-CRP was associated with worse cognitive performance at baseline but not over the ten-year follow-up among healthy participants (Lewis & Knight, 2021). Further, the authors identified a potential protective factor of raised CRP levels, with the rate of cognitive deterioration being less among the oldest-old who also had dementia. Another US-based study (Health and Aging Brain Among Latino Elders, HABLE) of approximately 330 healthy community-dwelling older Mexican Americans found a negative cross-sectional association between serum levels of CRP and performance verbal on lexical fluency (FAS) tasks, but not for any other measure (Vintimilla et al., 2019). The Framingham Heart Study evaluated chronically

raised low-grade inflammation based on raised serum CRP values in a cohort of around 2600 participants over 17 years and concluded that those with raised CRP levels and the Alzheimer's Disease-associated allele ApoE4 were associated with an increased risk of developing dementia (Tao et al., 2018). A study of CRP and long-term cognitive ability indicated that cardiovascular disease patients with raised levels of CRP were associated with poorer global cognitive ability, executive function, and attentional ability (Weinstein et al., 2017).

In sum, epidemiological studies show partial support for a negative relationship between chronic higher CRP levels (serum or plasma-based) and cognitive ability, but only cross-sectionally, not longitudinally. This still leaves much room for exploring how acute states of systemic inflammation, as they may accumulate over the lifetime, may affect cognition among thorax surgery patients.

Leukocytes

For Leukocyte (LZ) count, there was also an enormous increase from the presurgery to post-surgery level in each study. Based on the correlational analysis in Study 1, there was a negative association between the peak LZ value and MMSE Score prior to OP. No associations were found between LZ level and either RBANS or MMSE in Study 2 and none with MMSE in Study 3. Likewise, no zero-order correlations were found for postoperative cognition in any of the three studies for LZ level. Using hierarchical regression analyses for leukocyte count and total scores of post-operative MMSE in both Studies 2 and 3 yielded no associations. These findings align with Ramlawi et al.'s (2006) findings, which also found no difference in presurgery cognitive impairment and perioperative serum leukocyte count. Three other studies also reported leukocyte count and cognitive results, but only independently and not their associations: Christiansen et al. (2016), Fitch et al. (1999), and Günther et al. (2013).

MMRM modeling yielded additional information about the relationships between leukocyte count and cognition. In Study 1, MMRM indicated that the presurgery LZ level combined with time was a significant predictor of RBANS total score. In Study 2, MMRM analysis yielded LZ rise as a predictor of MMSE Score. Unfortunately, the dataset for Study 3 yielded no significant predictors of rise, rise*time, or peak, although the number of data points in Study 3 did not allow a full evaluation of all Leukocyte Count parameters.

The greater literature supports these results in both healthy populations and patient cohorts. For example, a cross-sectional report of older healthy adults in Taiwan (Age M±SD: 70.37±7.11 years) indicated that even within normal range leukocyte count, higher levels of leukocytes were associated with worse psychomotor speed performance (Kao et al., 2011b). A longitudinal study of US Americans involving over 12,000 participants over 20 years with normal range levels of leukocyte count indicated that higher levels in midlife negatively correlated with greater longitudinal changes in measures of cognition, especially memory (Walker et al., 2019). An analysis of over 2.000 German participants in the Study of Health in Pomerania (52.4±13.7 years of age) found that higher white blood counts were associated with greater imaging markers of brain aging (Janowitz et al., 2020).

Further Biomarkers

Only Study 1 assessed a larger panel of inflammatory biomarkers for which data collection was sufficient for analysis in the same manner as CRP and LZ with presurgery and postsurgery peak parameters. All three inflammatory parameters showed associations with cognitive performance: both rise and peak levels of Procalcitonin (PCT) and Interleukin-6 (IL-6) were meaningful predictors of RBANS total score; Interleukin-8 (IL-

8) peak and peak*time parameters were also predictors. These findings are novel in that, while some studies assessed these parameters and cognitive outcomes to date, no studies have directly compared these parameters and long-term cognition in thorax surgery patients. Next, these findings will be contextualized for each biomarker separately within the framework of existing literature.

Procalcitonin

The zero-order negative correlations for PCT and cognitive ability in Study 1 were found for the 3-month postoperative RBANS score, but this association disappeared by Month 12. Thus, the lack of correlation at Month 12 could have been due to the follow-up attrition rates or the fact that most patients were still in a recovery stage, which stopped by month 12. It does not negate the finding; however, PCT could be used as a marker for future study of inflammatory response. No studies of thorax surgery patients included PCT as a measure. However, support for levels of PCT as a marker of cognitive integrity has been shown in numerous reports about acute brain dysfunction in critically ill patients (McGrane et al., 2011). PCT has been proposed as a marker of acute brain injury in many other clinical populations, such as Sepsis (Haasper et al., 2010; Tsygankova et al., 2021) and Covid-19 (Hu et al., 2020; Sari et al., 2022). On the other hand, one study of CABG patients reported a lack of association between PCT level and short-term (7d post-surgery) cognitive decline (Nemeth et al., 2017). Other than Nemeth et al. (2017) and Study 1 in this thesis, it appears that this comparison has not been made.

Interleukin 6

Both Study 1 and Study 3 measured IL-6 in the perioperative period. In Study 1, there was a dynamic increase in IL-6 levels from 67% pathologically high prior to surgery to 99% pathologically high peak levels after surgery. In the case of Study 3, there was

data for only about 60% of the sample and only at the time before surgery, making it impossible to assess any dynamic shift post-surgery. The IL-6 levels determined prior to surgery were all in the normal range. In Study 1, the correlational analysis revealed a strong negative correlation between peak IL-6 levels and 3-month postsurgery RBANS level. Study 1 further indicated that rise and peak values post-surgery were individually predictive of RBANS performance and that the association with cognition was negative using MMRM analysis. There was an absence of difference in the trajectory of the cognitive performance over time, so this difference may be due to an underlying yet undiscovered third variable to do with physical health.

A negative relationship between prior cognitive ability and later plasma-based IL-6 levels among cardiac surgery patients was found by Pool et al. (2016). Even though six studies of thorax surgery patients covered in the systematic literature review at the outset of this thesis assessed IL-6 and cognition, except for Poole et al. (2006), none directly compared these data points. It should be said that plasma-based IL-6 is not directly comparable to serum-based IL-6 assessments used in Studies 1 and 3. Saxena et al. (2020) found an increase in IL-6 and cognitive impairment six weeks later in their heart surgery patients; however, they did not directly compare these parameters. Heyer et al. (2002) likewise made no comparison between IL-6 data and cognitive data, although both were assessed in their study, nor did Saxena et al. (2020), Skrabal et al. (2006), Uhle et al. (2018) or Westaby et al. (2001).

However, in another related cohort of patients with sepsis-induced brain dysfunction, as defined by coma or delirious state during acute sepsis (or blood poisoning), IL-6 in the peri-intensive period was also associated with high mortality rates (Orhun et al., 2019). In that study, a small portion (23%, 20 of 86) also received a brief cognitive screen (MMSE). In correlational analysis, the authors did not find an association between IL-6

and MMSE scores. Compared to other pre-clinical, i.e., animal models of sepsis, acute raised levels of IL-6 performance are commonly found to be detrimental to cognitive tasks among mice and rats (Barichello et al., 2019). Hence, Study 1 in this thesis is the first robust analysis of sterile (i.e., non-septic) acute IL-6 dynamic shift and long-term cognition.

Interleukin 8

No simple associations between IL-8 levels and cognitive performance at any time point in Study 1 using mere correlational analysis. In contrast, using MMRM modeling, both peak IL-8 and the interaction term IL-8 peak*time were significant predictors of the total RBANS score. Concretely, for each increase in the peak level of IL-8 by 100 pg/ml, there was a decrease in RBANS total score at any time point of -2.7 points based on REML. In addition, the trajectory of cognitive performance also depended on the peak IL-8 score.

Hence, MMRM analysis appears to be a superior method to examine long-term data in which great inter and intraperson variability can exist. Perhaps also, IL-8 could be a better predictor of cognitive outcomes than other biomarkers, at least in this population. This finding appears to be unique in the literature on systemic inflammation and thorax surgery patients. Although Mathew et al. (2009) assessed serum-based IL-8 and cognition, no comparison was made between these data. Orhun et al. (Orhun et al., 2019) also examined IL-8 in conjunction with a small portion of sepsis patients with acute brain dysfunction. As with IL-6, the authors found no zero-order correlation to the MMSE score. As with the previously described comparison to IL-6, this study suffered from severe truncation of data and potential bias due to only 23% of the cohort having been tested cognitively.

In the context of previous research on the interconnections between inflammatory biomarkers and cognitive performance, it is clear that no one inflammatory biomarker can tell the whole story of inflammation and cognition. It is also clear that patients undergoing thorax surgery who may be at higher risk of impaired cognition could be identified via serum-based inflammatory response, even if the causal pathways are unclear. It is becoming clear among other patient groups, such as Covid-19 patients, that the same serum-based biomarkers studied here may also be associated with disease progression or severity (Ponti et al., 2020).

Limitations

One of the intrinsic limitations in these studies was the heterogeneity of timing and type of biomarkers used. In fact, across the literature reviewed at the outset of this study, the biomarker and cognitive research field was immensely heterogeneous and largely unsynthesized. Hence, this makes direct comparison across studies quite difficult. It is not the case that each biomarker is equivalent to the other. Each biomarker represents one aspect of the body's immune answer to surgical trauma.

There are several limitations across these studies. One is the extreme inconsistency of sample-taking in Study 3, so post-hoc analyses were necessary using data from patient files. Thus, the full panel of biomarkers was assessed in that study only for about 20 patients, not enough to use in analysis or long-term comparisons of cognitive ability.

The diagnosis of SIRS, a clinical biomarker of inflammation, was not assessed consistently across studies. This means that some over or underrepresentation of this phenomenon may bias results. The very small sample size of Study 3 made it hard to do justice to this diagnosis. In addition, the clinical syndrome of SIRS (systemic inflammatory response syndrome) has now been deemed obsolete by the medical community (Singer et al., 2016).

In addition, the three studies were all each conducted in a single center. Especially for Study 3, this meant that sample sizes were small. The fact that each study was conducted at a university teaching hospital also may have restricted the types of patients to those with more education and worse health than patients in other settings. Further, the first two studies were not conceptualized as cognitive studies, but rather cognition was assessed as a safety measure in Study 1, and as a correlate of delirium in Study 2.

These cytokines were only thoroughly assessed in Study 1. Unfortunately, although Study 3 also assessed PCT and IL-6, blood draws were so highly inconsistent, and follow-up data points in the perioperative period were largely missing, so no further analysis was possible for several biomarkers in Study 3. The only consistent biomarkers across studies were SIRS, C-reactive protein, and Leukocyte Count. Whether these inflammatory biomarkers represent the direct influence of inflammatory states and acute events on cognition would require larger studies to confirm.

Since these studies can only show associations at a group level, the individual diagnostic value of measuring inflammatory biomarkers also warrants further study. In addition, the pathophysiology of inflammatory response and its consequences for brain integrity can only be presumed. Further translational research will be required.

Conclusion

This set of studies reveals several interconnections between chronic inflammatory levels and acute-stage inflammatory responses to surgery and cognitive performance. Medically, it is important to state that this is so in the absence of infection. At baseline, the group average among patients in Studies 1 and 2 corresponded with cognitive impairment at around 1.5 standard deviations below the norm (as measured by MMSE and RBANS). Long-term cognitive impairments among thorax surgery patients were associated with chronic inflammation as operationalized by presurgery levels of Leukocytes and

Interleukin-6 in Study 1 and presurgery C-reactive protein levels in Study 3. In contrast, higher presurgery IL-6 and Leukocyte Count indicated better cognitive performance in Study 3. There were no correlates between chronic inflammation and cognitive performance in Study 2. This indicates that no single biological marker should be relied on in future studies.

Hence, cognitive impairment among thorax surgery patients appears to be preexisting. The massive inflammatory response immediately after cardiac surgery does not modify the trajectory of cognitive performance over the follow-up period of 1 year.

Another important finding is a dramatic shift in the biological response to surgical insult. Hence in answer to the second of the guiding questions at the outset of this thesis, it can be said that the specific effect of acute systemic inflammation beyond chronic inflammation was demonstrated for peak levels of C-reactive protein in Study 1 and Study 2 using zero-order correlations and in Study 3 using MMRM. In addition, leukocyte rise was negatively associated with cognitive performance in Study 2. The clinical syndrome of SIRS was negatively associated with cognitive performance only in Study 1 but not in Study 2 or 3.

Overall, there did not appear to be multiplier effects between chronic and acute levels of inflammation in the biomarkers examined here. Some biomarkers showed a negative association at the presurgery level (LZ, CRP, IL-6) with cognition, and some showed a negative association of the acute increase after surgery (CRP, LZ, PCT, IL-8).

Hence, there is a need to use a diversified array of biological markers of inflammation, and these should also assess dynamic shifts pre to post-surgery. Large-scale epidemiological studies could include acute incidents of inflammation, such as pneumonia, sepsis, and Sars-CoV-2 infection, in addition to chronic measures.

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Appendix A Overview of Study Results

Table 1

Overview pathological values biomarkers, clinical and demographic characteristics across studies

Study Phase / Parameter	Study 1 *N = 125*	Study 2 *N = 224*	Study 3 *N = 31*
	Percentages of Biomarker		
Presurgery	CRP 61% PCT high 0% IL-6 67% IL-8 34% LZ 7%	CRP 43.4% LZ 7.1%	CRP study-based 40% / CRP patient file 35.3% PCT high 0% IL-6 0% NSE 20.6% S100 0% LZ study based missing / LZ patient file 2.9%
Postsurgery	CRP 97% PCT high 8% IL-6 99%, IL-8 74%, LZ 0%	CRP 93.4% LZ 96.7%	CRP patient file 91.2% LZ patient file 70.6 %
	Means and standard errors clinical and demographic information		
SIRS Diagnosis	42 (33.6%)	38 (34.8%)	4 (13.3%)
Surgery Duration (Minutes)	89.46 (3.845)	250.96 (6.919)	368.55 (16.578)
LOS ICU days	5.68 (1.170)	4.69 (.533)	4.86 (.818)
LOS Hospital	18.62 (1.558)	18.55 (.990)	12.62 (1.807)
Diabetes Type 2	38 of 125 (30.4%)	48 of 222 (21%)	9 (29%)
Delirium	38 of 125 (30.4%)	70 of 218 (31%)	0 of 20 (0%)
Mortality	9 (4.1%)	40 (32.0%)	0 (0%)
Age years	80.45 (.55)	70.02 (.686)	65.55 (1.433)
Sex (male)	52.8%	66.1%	70.9%
MMSE PreOP	25.3 (.317)	27.00 (.202)	29.23 (.195)
MMSE PostOP	not assessed	*Tel MMSE max 21 Pts.* 18.93 (.222)	*6M Post* 29.03 (.194)
RBANS PreOP	81.47(1.361)	*N= 46* 85.1 (1.893)	
RBANS PostOP	*12M RBANS* 83.70 (1.536)	*6M RBANS N= 46* 100.59 (2.131)	

Note. ICU = Intensive Care Unit; M = months; LOS = length of stay; PreOP = preoperative; PostOP = postoperative; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; IL = Interleukin; NSE = Neuron-specific enolase; ; S100 = calcium-binding protein.

Table 2

Overview correlations biomarkers and preoperative global cognition across studies

	Study 1		Study 2		Study 3
	N = 125		*N = 224*		*N = 31*
	RBANS	MMSE	RBANS	MMSE	MMSE
Parameters			N= 46		
SIRS	None	-.324**	none	none	none
CRP	None	none	none	none	none
LZ	None	Peak -.231*	none	none	none
PCT	None	none			none
IL-6	None	none			none
IL-8	None	none			none
NSE					none
S100					none

Note. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; PCT = Procalcitonin; IL = Interleukin; NSE = Neuron-specific enolase; ; S100 = calcium-binding protein.

** p < .05. ** p < .01.*

Table 3

Overview correlations biomarkers and postoperative global cognition across studies

	Study 1		Study 2		Study 3	
	N = 125		*N = 224*		*N = 31*	
	3M RBANS	12M RBANS	RBANS	6M MMSE	3-4M MMSE	6M MMSE
Parameters			N= 46			
SIRS	none	None	none	none	none	none
CRP	Peak -.226*	None	none	Peak -.114* Rise -.108*	none	none
LZ	none	None	none	none	none	none
PCT	Presurgery -.199* Peak -.219*	None			none	none
IL6	none	None			none	none
IL8	none	None			none	none
NSE					none	none
S100					none	none

Note. Rise = Difference between presurgery and peak level. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; PCT = Procalcitonin; IL = Interleukin; NSE = Neuron-specific enolase; ; S100 = calcium-binding protein.

** p < .05. ** p < .01.*

Table 3

Overview main effects biomarkers in hierarchical regression preoperative MMSE across studies

	Study 1 *N = 125*	Study 2 *N = 224*	Study 3 *N = 31*
Parameters	*Sig.*	*Sig.*	*Sig.*
CRP			
Presurgery		*n.s.*	*n.s.*
Peak		*n.s.*	*n.s.*
Rise		*n.s.*	*n.s.*
Peak x Rise		*n.s.*	*n.s.*
LZ			
Presurgery		*n.s.*	*n.s.*
Peak		*n.s.*	*n.s.*
Rise		*n.s.*	*n.s.*
Presurgery x Rise		*n.s.*	*n.s.*

Note. Rise = Difference betseen presurgery and peak level. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; IL = Interleukin.

** p < .05. ** p < .01. *** p < .001*

Table 4

Overview main effects biomarkers in hierarchical regression postoperative MMSE across studies

	Study 1 *N = 125*	Study 2 *N = 224*	Study 3 *N = 31*
Parameters	*Sig.*	*Sig.*	*Sig.*
SIRS		*n.s.*	*n.s.*
CRP			
Presurgery		*n.s.*	*n.s.*
Peak		*n.s.*	*n.s.*
Rise		*n.s.*	*n.s.*
Peak x Rise		*n.s.*	*n.s.*
LZ			
Presurgery		*n.s.*	*n.s.*
Peak		*n.s.*	*n.s.*
Rise		*n.s.*	*n.s.*
Presurgery x Rise		*n.s.*	*n.s.*

Note. Rise = Difference betseen presurgery and peak level. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; IL = Interleukin.

** p < .05. ** p < .01. *** p < .001*

Table 5

Main effects from MMRM analyses biomarkers and cognition across studies

Parameters	Study 1 (RBANS) *N = 125*	Study 2 (MMSE) *N = 46*	Study 3 (MMSE) *N = 31*
	Sig.	*Sig.*	*Sig.*
SIRS	.033*	*n.s.*	*n.s.*
SIRS x Time	*n.s.*	*n.s.*	*n.s.*
CRP			
Presurgery	*n.s.*	*n.s.*	.001**
Presurg.x Time	*n.s.*	*n.s.*	<.001***
Rise	*n.s.*	*n.s.*	<.001***
Rise xTime	*n.s.*	*n.s.*	<.001***
Peak	.018*	*n.s.*	<.001***
Peak xTime	*n.s.*	*n.s.*	<.001***
LZ			
Presurgery	*n.s.*	*n.s.*	x
Presurg.x Time	.032*	*n.s.*	x
Rise	*n.s.*	.009**	*n.s.*
Rise xTime	*n.s.*	*n.s.*	*n.s.*
Peak	*n.s.*	*n.s.*	*n.s.*
Peak xTime	*n.s.*	*n.s.*	x
PCT			
Presurgery	*n.s.*		
Presurg.x Time	*n.s.*		
Rise	.054		
Rise xTime	*n.s.*		
Peak	.022*		
Peak xTime	*n.s.*		
IL6			
Presurgery	.058		
Presurg.x Time	*n.s.*		
Rise	.021*		
Rise xTime	*n.s.*		
Peak	.015*		
Peak xTime	*n.s.*		
IL8			
Presurgery	*n.s.*		
Presurg.x Time	*n.s.*		
Rise	*n.s.*		
Rise xTime	*n.s.*		
Peak	.006**		
Peak xTime	.043*		

Note. Rise = Difference betseen presurgery and peak level. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; MMSE = Mini-Mental Status Examination; SIRS = Systemic Inflammatory Response Syndrome; CRP = C-reactive Protein; LZ = Leukocyte Count; IL = Interleukin.

** p < .05. ** p < .01. *** p < .001*

Appendix B Study 1

Missing Value Analysis SPSS Output

Table 1. Univariate Statistics

	N	Mean	Std. Deviation	Missing		No. of Extremes[a]	
				Count	Percent	Low	High
MMSE_E1	125	25.30	3.545	0	.0	7	0
TOT_E1	125	81.47	15.215	0	.0	0	1
TOT_E2	110	85.50	17.390	15	12.0	3	3
TOT_E3	104	83.17	15.376	21	16.8	0	0
TOT_E4	97	83.70	15.123	28	22.4	0	0
Max_CRP	125	84.015	46.7946	0	.0	0	3
Max_PCT	123	.8982	2.54298	2	1.6	0	15
Max_IL6	123	151.7146	672.54073	2	1.6	0	12
Max_IL8	123	42.1203	80.66938	2	1.6	0	14
Max_LZ	123	19.4841	91.22618	2	1.6	0	6
SIRS	124			1	.8		

*a. Number of cases outside the range (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

Table 2. Summary of Estimated Means

	MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
All Values	25.30	81.47	85.50	83.17	83.70	84.015	.8982	151.7146	42.1203	19.4841
EM	25.30	81.47	83.88	81.92	81.53	84.015	.8805	146.7843	41.4306	19.5007

Table 3. Summary of Estimated Standard Deviations

	MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
All Values	3.545	15.215	17.390	15.376	15.123	46.7946	2.54298	672.54073	80.66938	91.22618
EM	3.545	15.215	18.175	15.811	15.631	46.7946	2.54523	673.32611	80.80291	91.21693

Table 4. Separate Variance t Testsa

		MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
TOT_E2	t	1.7	3.1	.	2.5	.	-.4	-1.4	-1.1	-1.1	.5
	df	15.3	17.7	.	1.1	.	15.4	13.1	12.0	12.4	117.4
	P(2-tail)	.103	**.007**	.	.218	.	.723	.199	.281	.305	.596
	# Present	110	110	110	102	97	110	110	110	110	110
	# Missing	15	15	0	2	0	15	13	13	13	13
	Mean(Present)	25.60	83.00	85.50	83.47	83.70	83.200	.7459	84.3045	36.9809	20.0127
	Mean(Missing)	23.13	70.27	.	68.00	.	89.993	2.1869	722.1077	85.6077	15.0115
TOT_E3	t	1.6	2.5	.4	.	.	-1.0	-1.0	-1.1	-.9	.7
	df	22.4	27.9	8.2	.	.	24.2	21.8	18.0	19.6	107.3
	P(2-tail)	.132	**.017**	.665	.	.	.341	.317	.291	.374	.484
	# Present	104	104	102	104	97	104	104	104	104	104
	# Missing	21	21	8	0	0	21	19	19	19	19
	Mean(Present)	25.63	83.04	85.71	83.17	83.70	81.732	.7761	86.4221	37.6413	20.5504
	Mean(Missing)	23.71	73.71	82.87	.	.	95.324	1.5668	509.1053	66.6368	13.6479
TOT_E4	t	1.7	3.3	.7	2.8	.	-1.1	-1.6	-1.2	-1.0	.8
	df	33.3	43.7	15.9	7.7	.	38.0	30.5	25.0	29.6	98.3
	P(2-tail)	.099	**.002**	.479	**.025**	.	.259	.131	.257	.339	.406
	# Present	97	97	97	97	97	97	97	97	97	97

# Missing	28	28	13	7	0	28	26	26	26	26
Mean(Present)	25.67	83.79	85.92	84.01	83.70	81.145	.6629	82.1381	37.2000	21.3363
Mean(Missing)	24.04	73.43	82.38	71.57	.	93.957	1.7762	411.2885	60.4769	12.5742

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 5. Crosstabulations of SIRS as Indicator Variable

			Total	0	1	Missing SysMis
TOT_E2	Present	Count	110	78	32	0
		Percent	88.0	95.1	76.2	.0
	Missing	% 999	12.0	4.9	23.8	100.0
TOT_E3	Present	Count	104	75	29	0
		Percent	83.2	91.5	69.0	.0
	Missing	% 999	16.8	8.5	31.0	100.0
TOT_E4	Present	Count	97	71	26	0
		Percent	77.6	86.6	61.9	.0
	Missing	% 999	22.4	13.4	38.1	100.0

Indicator variables with less than 5% missing are not displayed.

Table 6. Percent Mismatch of Indicator Variables.a.b

	TOT_E2	TOT_E3	TOT_E4
TOT_E2	12.00		
TOT_E3	8.00	16.80	
TOT_E4	10.40	5.60	22.40

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 7. Missing Value Codes in Pattern Tables

	Pattern Codes
	A
MMSE_E1	999
TOT_E1	999
TOT_E2	999
TOT_E3	999
TOT_E4	999
Max_CRP	999.0
Max_PCT	999.00
Max_IL6	999.00
Max_IL8	999.00
Max_LZ	999.00
SIRS	999

In the tables that follow displaying individual cases. the following symbols are used:

+. Extremely high value
-. Extremely low value
S. System-missing value
A. First type of user-missing value
B. Second type of user-missing value
C. Third type of user-missing value

Table 8. Data Patterns (all cases)

Case[a]	# Missing	% Missing	Missing and Extreme Value Patterns										
			MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ	SIRS
21	8	72.7			A	A	A		S	S	S	S	S
179	3	27.3			A	A	A						
95	7	63.6			A	A	A		S	S	S	S	
138	1	9.1					A						
133	2	18.2			A		A						
173	2	18.2			A		A						
116	2	18.2	-			A	A						
175	2	18.2				A	A						
141	2	18.2				A	A						
86	1	9.1					A		+				
81	2	18.2				A	A						
22	2	18.2				A	A						
144	0	.0			+								
225	0	.0											
200	0	.0											
12	0	.0											
177	0	.0											
99	0	.0									+		
83	0	.0											
183	0	.0											
206	0	.0											
51	0	.0											
47	0	.0											
214	0	.0											
190	0	.0											
103	0	.0											
152	0	.0											
106	0	.0							+			+	
218	0	.0											
199	0	.0											
165	0	.0											
227	0	.0									+		
53	0	.0											
85	0	.0											
213	0	.0											
169	0	.0											
54	0	.0											
119	0	.0											
170	0	.0											
237	0	.0											
192	0	.0											
171	0	.0											
145	0	.0											
93	0	.0									+		
129	0	.0											
153	0	.0											
149	0	.0											
205	0	.0	-										
41	0	.0											
50	0	.0											
34	0	.0											

96	0	.0							+					
216	0	.0												
203	0	.0												
172	0	.0												
204	0	.0										+		
38	0	.0												
104	0	.0							+					
31	0	.0			+									
228	0	.0									+	+		

Table 8. Data Patterns (all cases) continued

Case[a]	# Missing	% Missing	Missing and Extreme Value Patterns											
			MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ	SIRS	
236	0	.0												
91	0	.0									+			
230	0	.0							+					
48	0	.0												
184	0	.0												
146	0	.0												
24	0	.0												
17	0	.0												
215	0	.0												
161	0	.0												
163	0	.0												
46	0	.0												
148	0	.0								+				
147	0	.0									+			
130	0	.0												
98	0	.0												
193	0	.0							+					
195	0	.0												
191	0	.0								+				
80	0	.0												
166	0	.0												
101	0	.0												
36	0	.0												
55	3	27.3	-		A	A	A			+				
132	3	27.3	-		A	A	A							
10	2	18.2	-		-	A	A							
39	3	27.3			A	A	A					+		
13	3	27.3	-		A	A	A	+	+	+	+	+		
35	3	27.3			A	A	A							
15	3	27.3			A	A	A		+	+				
79	2	18.2				A	A							
26	1	9.1					A		+	+	+			
121	3	27.3			A	A	A							
8	1	9.1					A							
219	3	27.3			A	A	A		+	+	+	+		
7	1	9.1					A		+					
180	2	18.2				A	A							
49	3	27.3			A	A	A		+			+		
43	3	27.3			A	A	A							
94	0	.0												
92	0	.0												
155	0	.0									+			
23	0	.0										+		
151	0	.0												
154	0	.0												
118	0	.0						+						
198	0	.0												
211	0	.0												
45	0	.0												
189	0	.0												
207	0	.0												
238	0	.0												
229	0	.0												
84	0	.0												
164	0	.0	-		-				+	+	+			
11	0	.0		+	+				+	+	+			
185	0	.0								+				

168	0	.0											
136	0	.0											
150	0	.0						+					
20	0	.0											
88	0	.0											
87	0	.0											
117	0	.0											
82	0	.0			-					+	+	+	

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

a. Cases are sorted by CRP_48h.

Table 9. Missing Patterns (cases with missing values)

Case	# Missing	% Missing	Missing and Extreme Value Patterns[a]											
			MMSE_E1	TOT_E1	Max_CRP	SIRS	Max_PCT	Max_IL6	Max_IL8	Max_LZ	TOT_E2	TOT_E3	TOT_E4
138	1	9.1											A
86	1	9.1					+						A
26	1	9.1					+	+	+				A
8	1	9.1											A
7	1	9.1					+						A
173	2	18.2									A		A
133	2	18.2									A		A
179	3	27.3									A	A	A
55	3	27.3	-					+			A	A	A
132	3	27.3	-								A	A	A
39	3	27.3								+	A	A	A
13	3	27.3	-		+		+	+	+	+	A	A	A
35	3	27.3									A	A	A
15	3	27.3					+	+			A	A	A
121	3	27.3									A	A	A
219	3	27.3					+	+	+	+	A	A	A
49	3	27.3					+			+	A	A	A
43	3	27.3									A	A	A
175	2	18.2										A	A
79	2	18.2										A	A
10	2	18.2	-								-	A	A
81	2	18.2										A	A
116	2	18.2	-									A	A
180	2	18.2										A	A
22	2	18.2										A	A
141	2	18.2										A	A
95	7	63.6					S	S	S	S	A	A	A
21	8	72.7				S	S	S	S	S	A	A	A

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

a. Cases and variables are sorted on missing patterns.

Table 10. Tabulated Patterns

Number of Cases	Missing Patterns[a]										Complete if ...[b]
	MMSE_E1	TOT_E1	Max_CRP	SIRS	Max_PCT	Max_IL6	Max_IL8	Max_LZ	TOT_E2	TOT_E3	TOT_E4	
97												97
5											X	102
2									X		X	104
11									X	X	X	123
8										X	X	110

Patterns with less than 1% cases (1 or fewer) are not displayed.

a. Variables are sorted on missing patterns.

b. Number of complete cases if variables missing in that pattern (marked with X) are not used.

EM Estimated Statistics

Table 11. EM Means[a.b]

MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
25.30	81.47	83.88	81.92	81.53	84.015	.8805	146.7843	41.4306	19.5007

a. Little's MCAR test: Chi-Square = 43.972. DF = 35. Sig. = .142

b. The EM algorithm failed to converge in 25 iterations.

Table 12. EM Covariances[a.b]

	MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
MMSE_E1	12.568									
TOT_E1	31.678	231.509								
TOT_E2	33.323	209.769	330.326							
TOT_E3	30.641	191.838	232.651	249.987						
TOT_E4	30.665	198.537	239.924	236.196	244.318					
Max_CRP	-43.957	-123.337	-246.898	-200.903	-177.319	2189.7340				
Max_PCT	-.539	-3.722	-9.063	-7.832	-8.163	32.9924	6.47822			
Max_IL6	-138.116	-233.258	-2012.406	-8.422	-925.769	7934.9851	733.13327	453368.04813		
Max_IL8	-9.853	45.464	-262.740	-69.635	-112.621	1022.7939	81.46134	35824.01792	6529.11071	
Max_LZ	26.711	-25.336	33.535	144.794	55.848	127.1398	5.80096	180.70323	-105.20112	8320.52862

a. Little's MCAR test: Chi-Square = 43.972. DF = 35. Sig. = .142

b. The EM algorithm failed to converge in 25 iterations.

Table 13. EM Correlations[a.b]

	MMSE_E1	TOT_E1	TOT_E2	TOT_E3	TOT_E4	Max_CRP	Max_PCT	Max_IL6	Max_IL8	Max_LZ
MMSE_E1	1									
TOT_E1	.587	1								
TOT_E2	.517	.759	1							
TOT_E3	.547	.797	.810	1						
TOT_E4	.553	.835	.845	.956	1					
Max_CRP	-.265	-.173	-.290	-.272	-.242	1				
Max_PCT	-.060	-.096	-.196	-.195	-.205	.277	1			
Max_IL6	-.058	-.023	-.164	-.001	-.088	.252	.428	1		
Max_IL8	-.034	.037	-.179	-.055	-.089	.270	.396	.658	1	
Max_LZ	.083	-.018	.020	.100	.039	.030	.025	.003	-.014	1

a. Little's MCAR test: Chi-Square = 43.972. DF = 35. Sig. = .142

b. The EM algorithm failed to converge in 25 iterations.

Checking for Outliers: Boxplots

Figure 1. Boxplot of MMSE Pre-OP (Standard Values)

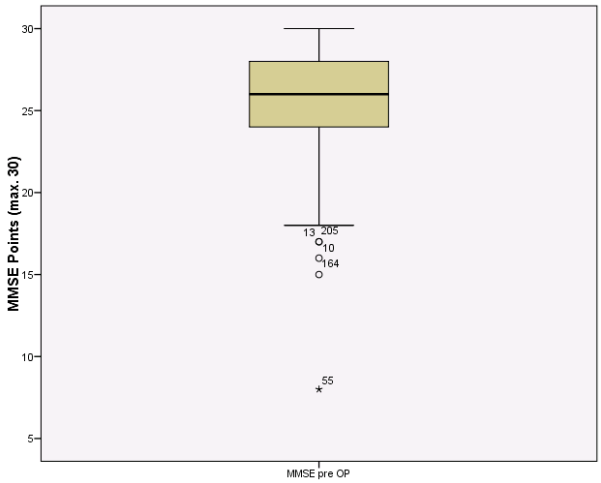


Figure 2. Boxplot of RBANS Pre-OP

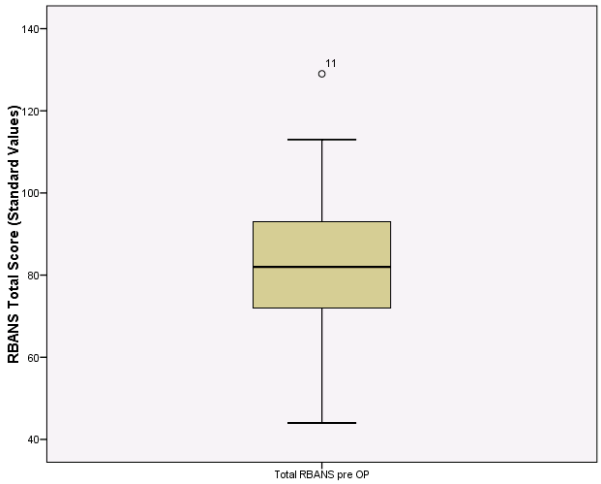


Figure 3. Boxplot RBANS 3 days post-OP

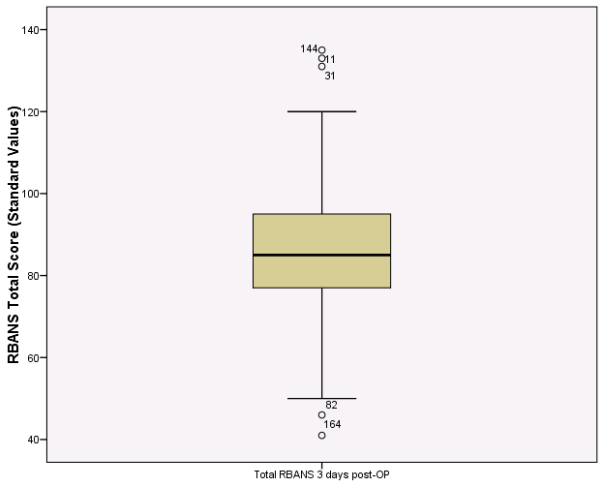


Figure 4. Boxplot RBANS 3 months post-OP

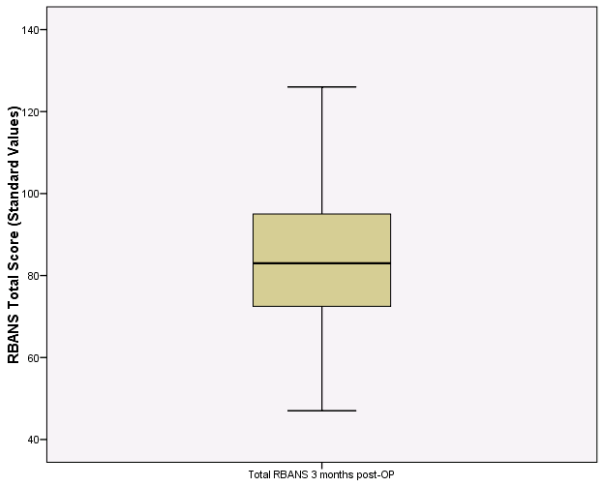


Figure 5. Boxplot RBANS 12 months post-OP

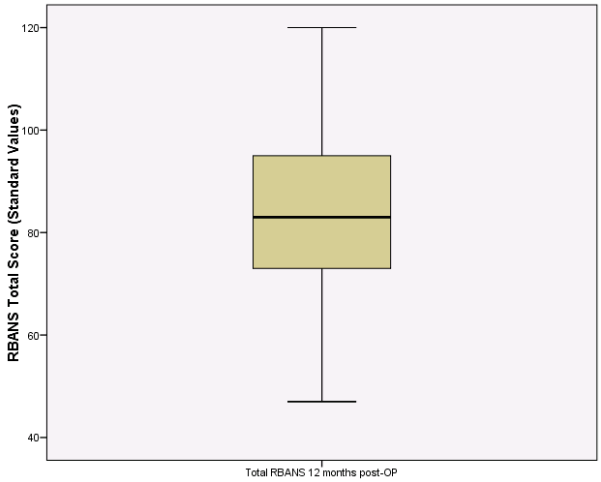


Figure 7. Boxplot maximum CRP

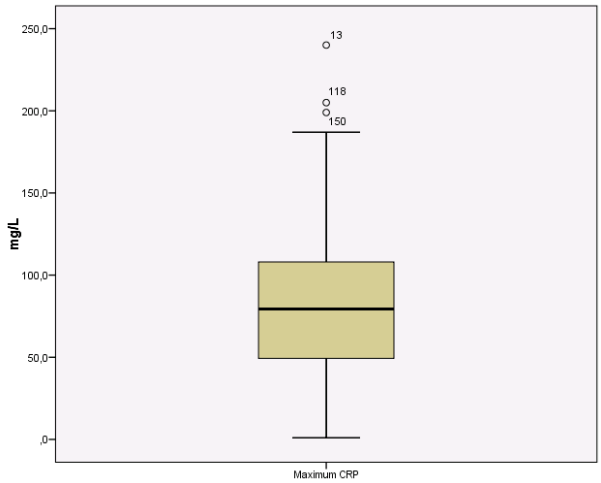


Figure 8. Boxplot of Maximum PCT

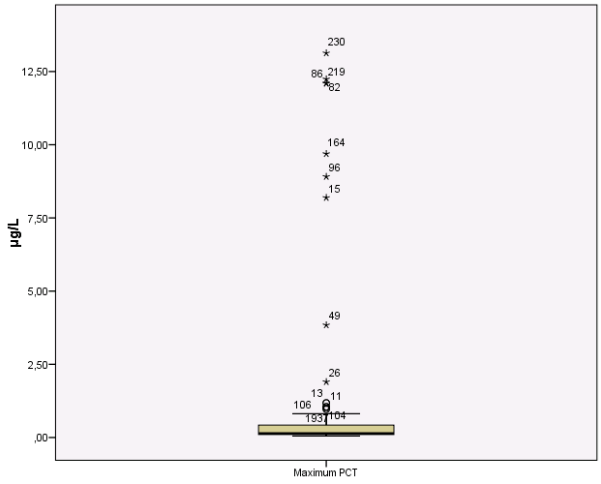


Figure 9. Boxplot of maximum IL-6

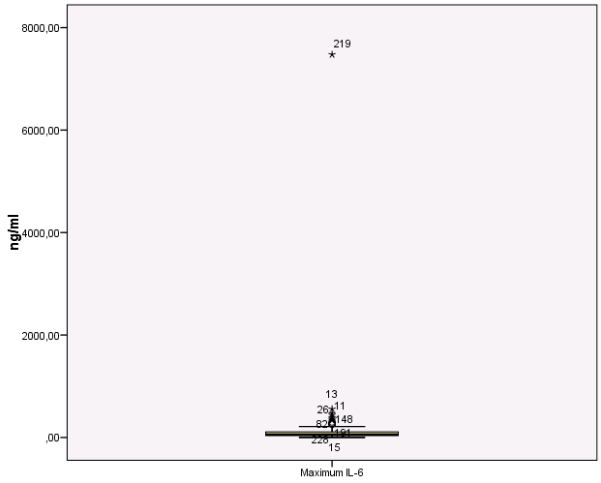


Figure 10. Boxplot of maximum IL-8

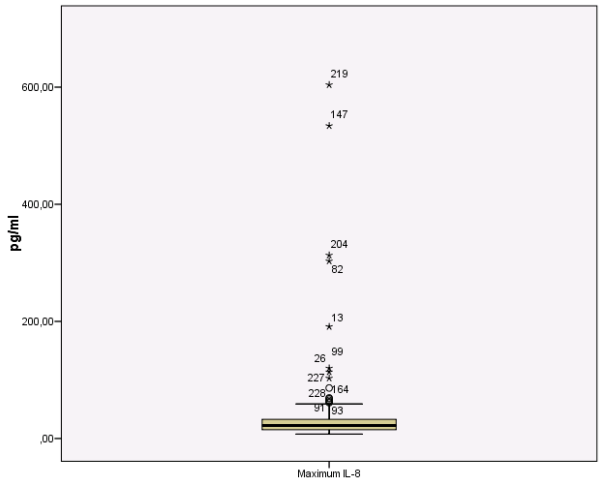
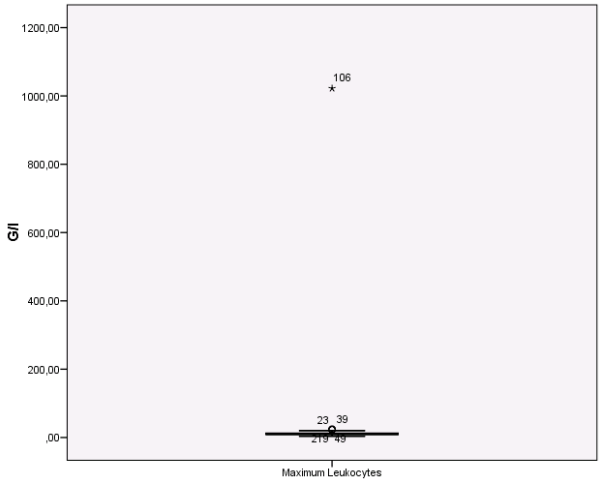


Figure 11. Boxplot of maximum Leukocytes (LZ)



Testing of Normality

Table 14. Tests of Normality for Cognitive Assessments

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
MMSE pre OP	.162	125	**.000**	.880	125	**.000**
Total RBANS pre OP	.059	125	.200*	.992	125	.695
Total RBANS 3 days post-OP	.094	110	**.018**	.977	110	.051
Total RBANS 3 months post-OP	.078	104	.131	.992	104	.832
Total RBANS 12 months post-OP	.073	97	.200*	.990	97	.665

**. This is a lower bound of the true significance.*

a. Lilliefors Significance Correction

Figure 12. Normal Q-Q Plot of MMSE Pre OP

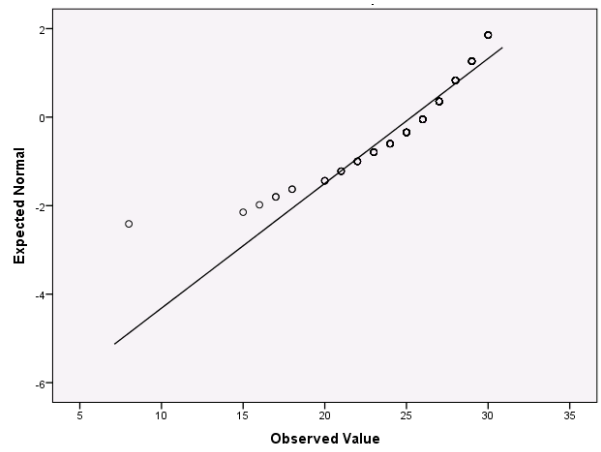


Figure 13. Detrended Normal Q-Q Plot of MMSE Pre OP

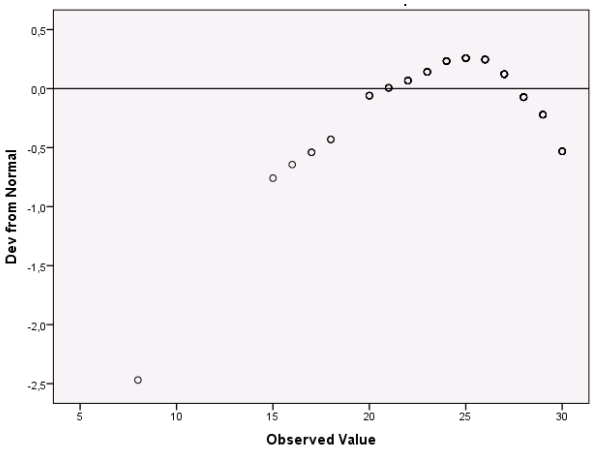


Figure 14. Normal Q-Q Plot of Total RBANS 3 days post OP

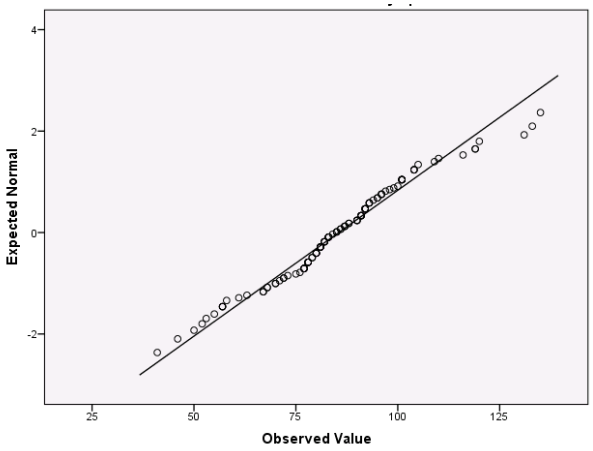


Figure 15. Detrended Normal Q-Q Plot of Total RBANS 3 days post-OP

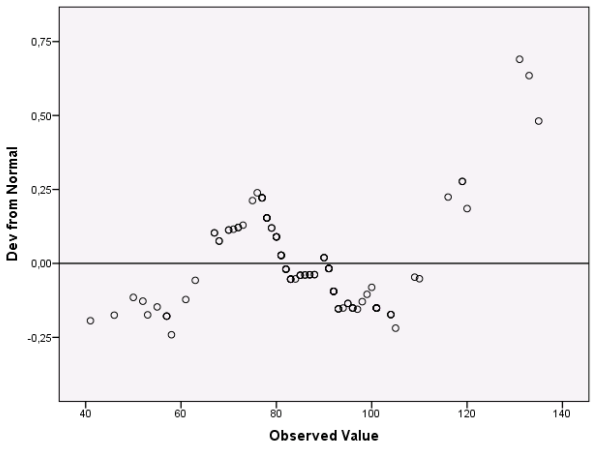


Figure 16. Normal Q-Q Plot of Total RBANS 3 months post OP

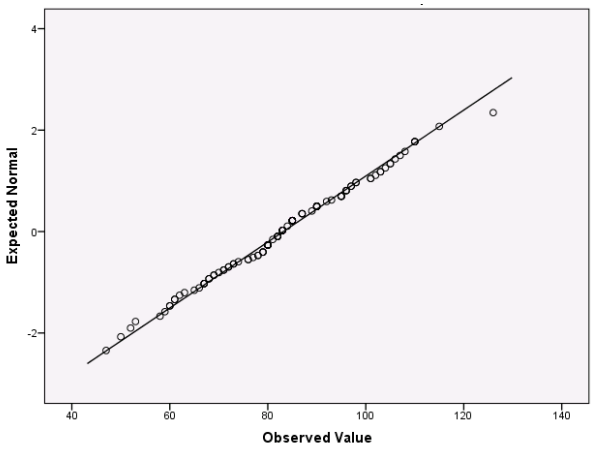


Figure 17. Detrended Normal Q-Q Plot of Total RBANS 3 months post-OP

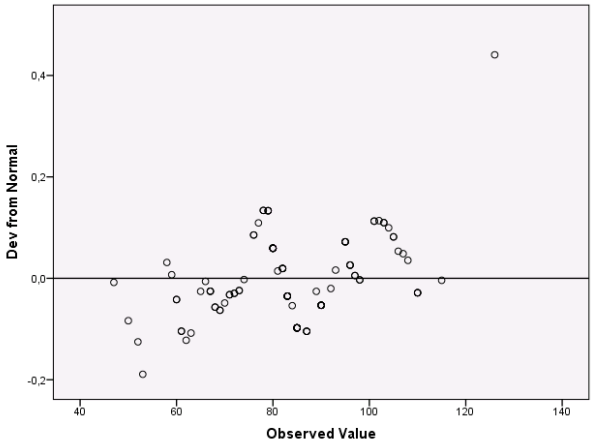


Figure 18. Normal Q-Q Plot of Total RBANS 12 months post OP

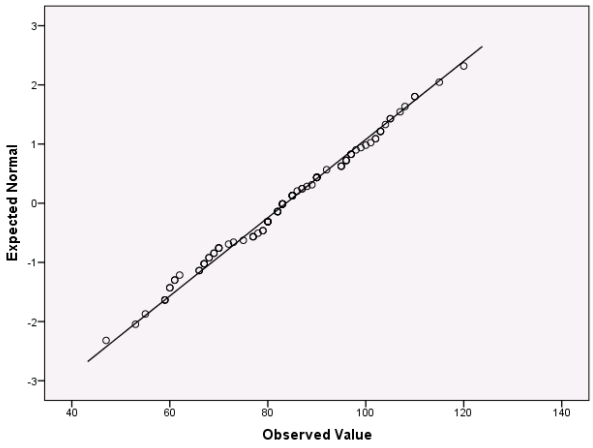
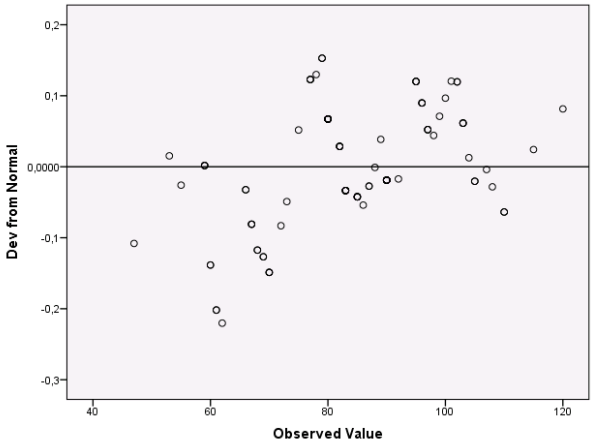


Figure 19. Detrended Normal Q-Q Plot of Total RBANS 12 months post-OP



Serum Biomarker Data

Table 15. Tests of Normality for Serum Biomarker Data[a]

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Maximum CRP	.076	125	.075	.969	125	**.006**
Maximum PCT	.394	123	**.000**	.340	123	**.000**
Maximum IL-6	.412	123	**.000**	.131	123	**.000**
Maximum IL-8	.339	123	**.000**	.356	123	**.000**
Maximum Leukocytes	.469	123	**.000**	.087	123	**.000**

a. Lilliefors Significance Correction

Figure 20. Normal Q-Q Plot of maximum CRP

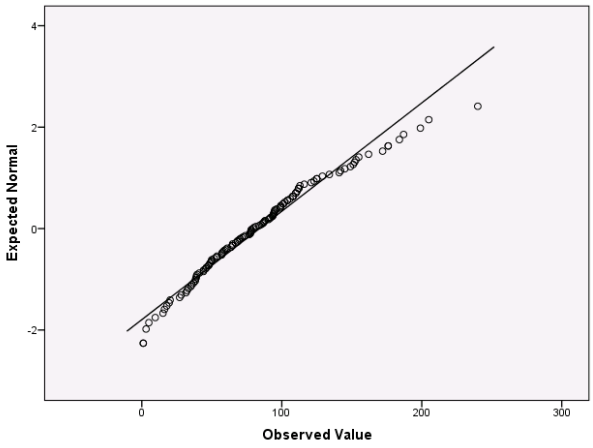


Figure 21. Detrended Normal Q-Q Plot of maximum CRP

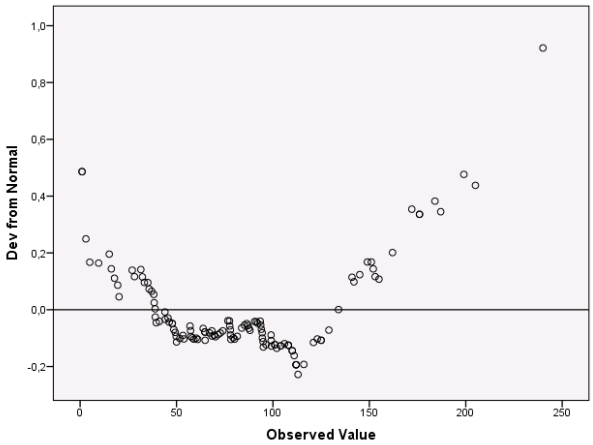


Figure 22. Normal Q-Q Plot of maximum PCT

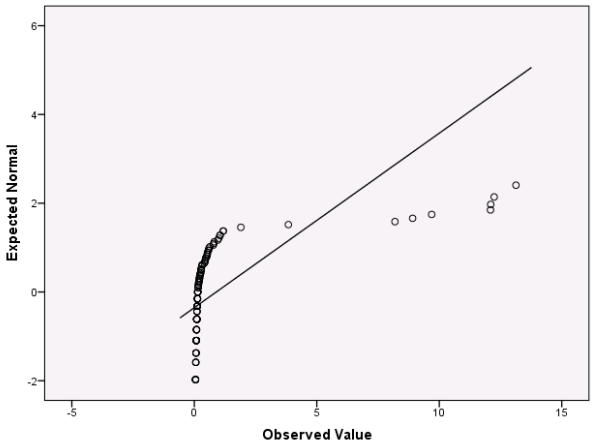


Figure 23. Detrended Normal Q-Q Plot of maximum PCT

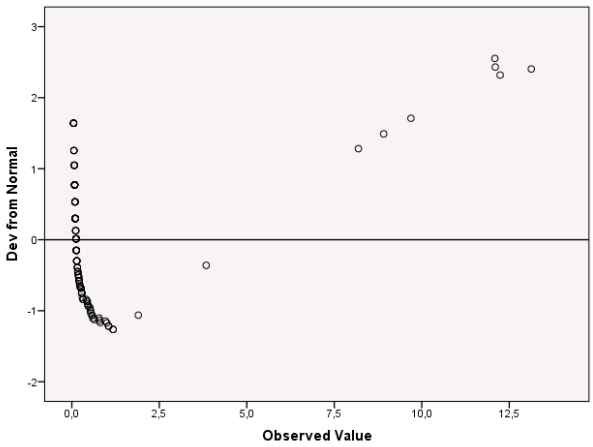


Figure 24. Normal Q-Q Plot of IL-6

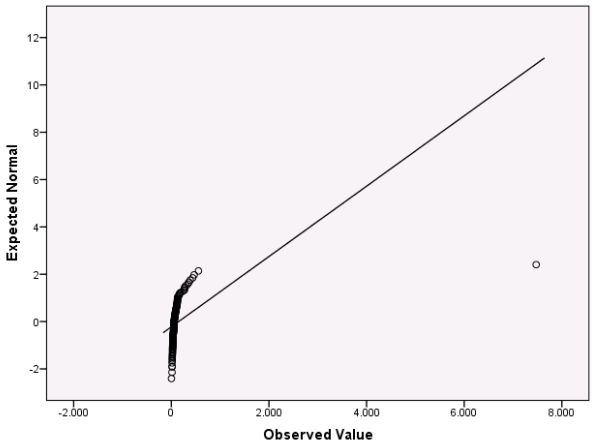


Figure 25. Detrended Normal Q-Q Plot of IL-6

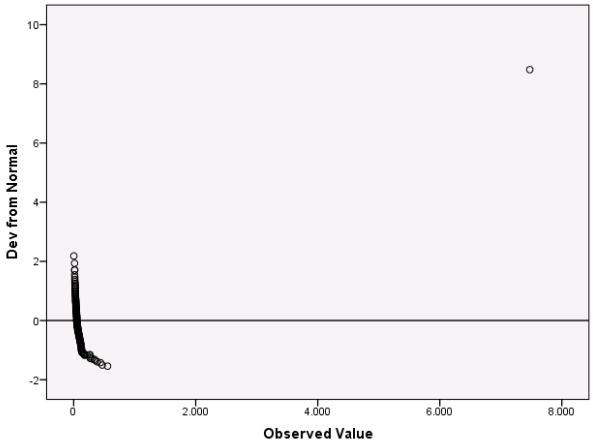


Figure 26. Normal Q-Q Plot of Leukocytes (LZ)

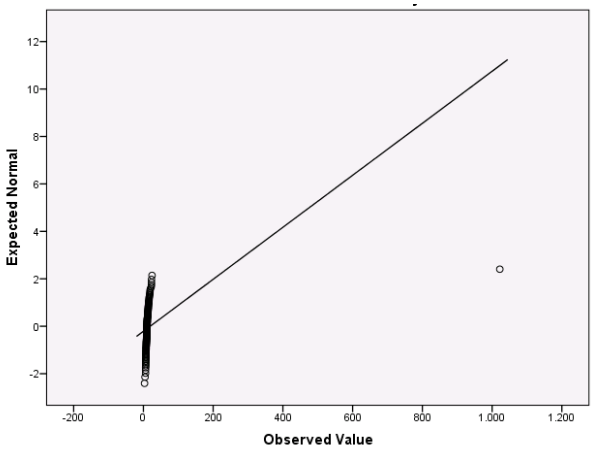
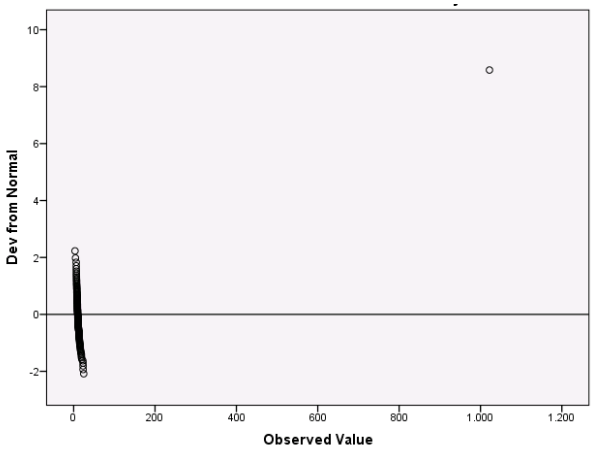


Figure 27. Detrended Normal Q-Q Plot of Leukocytes (LZ)



Grouped Data tests of normality Cognitive Data

Table16. Tests of Normality Cognitive Parameters Grouped Data (SIRS, no SIRS)[a]

	SIRS (2 or more Criteria)	Kolmogorov-Smirnova			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
MMSE pre OP	0	.193	71	.000	.913	71	.000
	1	.131	26	.200*	.929	26	.074
Total RBANS pre OP	0	.075	71	.200*	.986	71	.610
	1	.092	26	.200*	.982	26	.917
Total RBANS 3 days post-OP	0	.089	71	.200*	.973	71	.136
	1	.122	26	.200*	.966	26	.515
Total RBANS 3 months post-OP	0	.065	71	.200*	.986	71	.634
	1	.114	26	.200*	.979	26	.848
Total RBANS 12 months post-OP	0	.063	71	.200*	.986	71	.605
	1	.114	26	.200*	.982	26	.913

*a. Lilliefors Significance Correction *. This is a lower bound of the true significance*

Figure 28. Normal Q-Q Plot of MMSE pre OP No SIRS

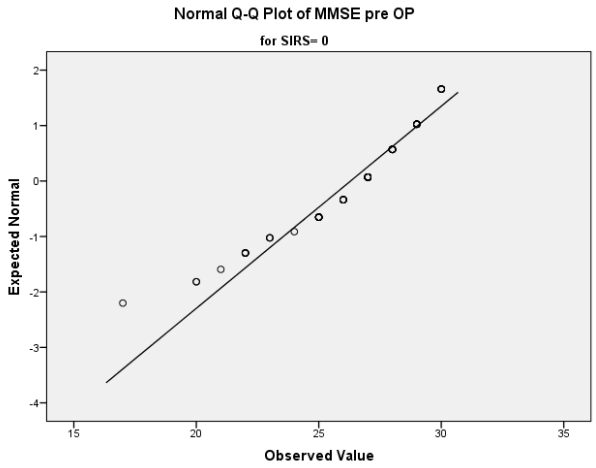


Figure 29. Detrended Normal Q-Q Plot of MMSE pre OP No SIRS

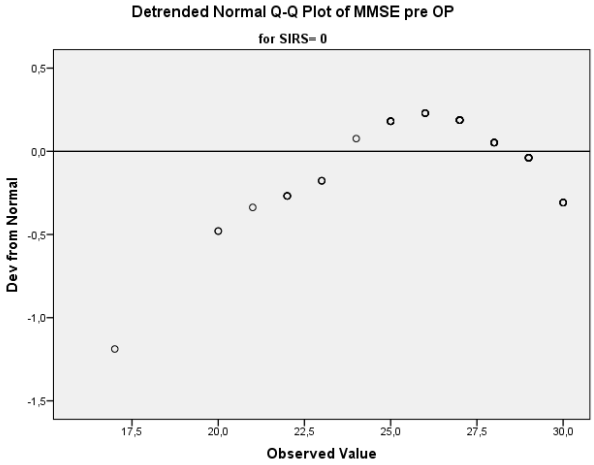


Figure 30. Normal Q-Q Plot of MMSE Pre OP SIRS

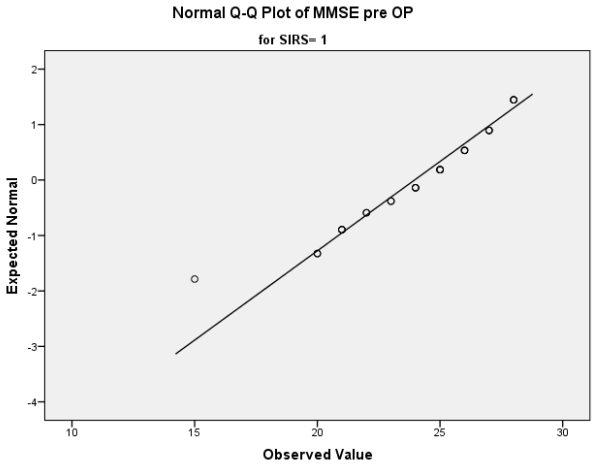
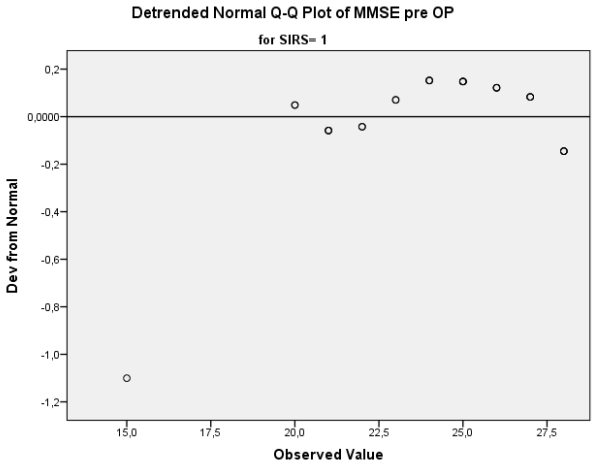


Figure 31. Normal Q-Q Plot of MMSE Pre OP SIRS



Transformations

Since the cognitive outcome data must be normally distributed for GLM analyses grouped and ungrouped, the following parameters were transformed to achieve normal distribution for two cognitive parameters

(see "**Testing of Normality**", above). Ungrouped data:

MMSE pre-OP

RBANS at 3 months

Grouped data: MMSE Pre OP no SIRS

Appendix C Study 2

Missing Value Analysis for all participants

Table 1. Univariate Statistics for all participants[a]

					Missing		No. of Extremes[a]	
		N	Mean	Std. Deviation	Count	Percent	Low	High
MMSE pre-OP	MMSE	224	27.05	2.966	2	.9	3	0
MMSE	Tel. post-OP	188	18.99	2.984	38	16.8	3	1
cytes	Leuko-	223	7.8924	6.95717	3	1.3	0	7
	CRP	219	8.2847	17.30184	7	3.1	0	23
bosis	Throm-	224	239.19	68.328	2	.9	0	5
Sepsis	SIRS or	219			7	3.1		
Sample	Blood	208			18	8.0		

a. Number of cases outside the range (Q1 - 1.5*IQR. Q3 + 1.5*IQR).

Table 2. Summary of Estimated Means for all participants

		MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
	Listwise	27.17	18.97	7.7564	8.1135	237.40
ues	All Val-	27.05	18.99	7.8924	8.2847	239.19
	EM	26.91	18.81	7.8085	8.8778	238.03
sion	Regres-	27.07	18.88	7.9029	8.3270	239.38

Table 3. Summary of Estimated Standard Deviations for all participants

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
Listwise	2.800	2.982	7.55873	17.82165	66.271
All Values	2.966	2.984	6.95717	17.30184	68.328
EM	3.031	3.043	6.84216	18.07731	68.418
Regression	2.958	3.097	6.91405	17.20346	68.199

Appendix D Study 3

Missing Value Analysis SPSS Output

Table 1. Univariate Statistics

	N	Mean	Std. Deviation	Missing		No. of Extremesa	
				Count	Percent		
Age	24	64.00	8.521	0	.0	0	0
Length_Surgery	24	278.79	73.818	0	.0	0	0
LOS_ICU	24	1.87	1.895	0	.0	0	1
LOS_Hosp	24	4.92	4.845	0	.0	0	1
Secondary_Edu_Yrs	24	9.83	1.949	0	.0	0	0
Tertiary_Edu_Yrs	24	3.25	1.032	0	.0	1	0
Edu_Yrs_Total	24	13.08	2.569	0	.0	0	0
BMI	24	27.0479	3.83279	0	.0	0	1
mmstot_V1	24	24.58	1.283	0	.0	1	1
mmstot_V4	24	29.04	.999	0	.0	0	0
mmstot_V5	24	29.13	.992	0	.0	1	0
VLMT_Learning_V5	24	41.50	10.653	0	.0	0	0
vlmtdg6r_V5	24	6.58	3.586	0	.0	0	0
vlmtdg7r_V5	24	7.25	3.566	0	.0	0	0
wms4vw1tot_V5	24	32.21	6.318	0	.0	0	0
wms4vw2tot_V6	13	27.92	8.883	11	45.8	0	0
TMT_A_V5	24	45.54	14.231	0	.0	1	2
TMT_B_V5	24	116.46	69.924	0	.0	0	3
sdmctot_V5	24	44.25	11.946	0	.0	0	0
vfatot_V5	24	20.96	5.953	0	.0	0	0
cervfg_V5	24	11.17	5.019	0	.0	0	0
wmsdsf_V5	24	7.00	1.888	0	.0	0	0
wmsdsb_V5	24	5.88	1.849	0	.0	2	1
BAI_Tot_V5	23	6.43	9.090	1	4.2	0	3
PTSS_10_Tot	23	16.61	7.216	1	4.2	0	0
PHQ_D_Somatic_Scale	24	3.96	4.080	0	.0	0	1
PHQ_D_Depression_Scale	24	3.88	3.893	0	.0	0	0
CRP_V1	21	3.4333	3.96413	3	12.5	0	1
CRP_V2	19	122.2316	84.77728	5	20.8	0	0
CRP_V3	1	19.0000	.	23	95.8	.	.
CRP_V4	19	3.9053	6.16581	5	20.8	0	2
CRP_V5	18	5.2278	7.90538	6	25.0	0	2
PCT_V1	21	.0590	.02047	3	12.5	0	1
PCT_V2	19	.6400	.58627	5	20.8	0	2
PCT_V3	1	.3000	.	23	95.8	.	.
PCT_V4	19	.0758	.02293	5	20.8	0	0
PCT_V5	18	.0739	.02893	6	25.0	0	0
NSE_V1	21	11.9952	4.84721	3	12.5	0	2
NSE_V2	19	18.2579	7.31341	5	20.8	0	0
NSE_V3	1	16.5000	.	23	95.8	.	.
NSE_V4	19	11.7368	3.01021	5	20.8	1	0
NSE_V5	18	11.2333	2.83777	6	25.0	0	0
S100_V1	21	.0571	.01927	3	12.5	0	0
S100_V2	19	.1595	.10860	5	20.8	0	3
S100_V4	19	.0537	.02290	5	20.8	0	2
S100_V3	1	.0500	.	23	95.8	.	.
S100_V5	18	.0544	.02617	6	25.0	0	0

Table 1. Univariate Statistics (cont'd)

	N	Mean	Std. Deviation	Missing		No. of Extremesa	
				Count	Percent		
IL_6_V1	21	4.1667	3.29262	3	12.5	0	2
IL_6_V2	19	123.5316	154.49703	5	20.8	0	1
IL_6_V3	1	32.8000	.	23	95.8	.	.
IL_6_V4	19	3.4000	2.52433	5	20.8	0	1
IL_6_V5	18	3.5333	2.54003	6	25.0	0	1
IL1_alpha_V1	21	.0600	.17187	3	12.5	.	.
IL1_alpha_V2	19	.0416	.09179	5	20.8	0	3
IL1_alpha_V3	2	.0100	.01414	22	91.7	0	0
IL1_alpha_V4	21	4.4010	19.98934	3	12.5	0	3
IL1_alpha_V5	19	.0274	.05414	5	20.8	0	4
IL1_beta_V1	21	.1129	.08100	3	12.5	0	0
IL1_beta_V2	19	.1274	.07460	5	20.8	0	0
IL1_beta_V3	2	.2500	.09899	22	91.7	0	0
IL1_beta_V4	21	.0700	.08820	3	12.5	0	3
IL1_beta_V6	14	.0714	.03959	10	41.7	0	0
TNF_alpha_V1	21	2.8200	1.19149	3	12.5	0	1
TNF_alpha_V2	19	2.7063	.97585	5	20.8	0	1
TNF_alpha_V3	2	5.6700	4.45477	22	91.7	0	0
TNF_alpha_V4	21	2.8486	1.07476	3	12.5	0	0
TNF_alpha_V5	19	3.0111	1.76861	5	20.8	0	1
LZ_V1	0	.	.	24	100.0	0	0
LZ_V2	24	10.2342	3.34957	0	.0	0	0
LZ_V3	2	9.5450	.96874	22	91.7	0	0
LZ_V4	0	.	.	24	100.0	0	0
LZ_V5	0	.	.	24	100.0	0	0
Sex	24			0	.0		

*a. Number of cases outside the range (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

Table 2. Pattern of missing and extreme values[a]

Case Number	Missing	% Missing	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Lern_Sum_V5	TMT_A_V5	TMT_B_V5	sdmtot_V5	sdmc-tot_V5	vfa-tot_V5	cer-vfg_V5	wmsdsf_V5	wmsdsb_V5	wmstot_V5	vlm-tdg1r	vlm-tdg5r	vlm-tdg6r	vlm-tdg7_tm	vlm-trecog_r	wms4vw1tot_V5	wms4vw2tot_V5	wms4we_V5	SIRSSYN
10	1	4.5																						C
27	1	4.5									+		+											C
25	1	4.5	-																				C	
26	1	4.5					+																C	
24	2	9.1	S									+									C	C		
32	22	100.0	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
33	22	100.0	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
34	22	100.0	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S

*- indicates an extremely low value, while + indicates an extremely high value. The area used (Q1 - 1,5*IQR, Q3 + 1,5*IQR).*

a. Cases and Variablen are sorted by pattern of missing values.

Table 3. Summary of Estimated Means

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Second-ary_Edu_Yrs	Ter-tiary_Edu_Yrs	Edu_Yrs_To-tal	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5	vlmtdg6r_V5
All Values		64.00	278.79	1.87	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50	6.58
EM		64.00	278.79	1.87	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50	6.58

Table 4. Summary of Estimated Means

	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5	PTSS_10_Tot	PHQ_D_Somatic_Scale	PHQ_D_Depression_Scale
Alle Werte	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43	16.61	3.96	3.88
Regression	32.21	28.86	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.50	16.64	3.96	3.88

Table 5. Summary of Estimated Means

	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4	PCT_V5	NSE_V1	NSE_V2	NSE_V3
Alle Werte	3.4333	122.2316	19.0000	3.9053	5.2278	.0590	.6400	.3000	.0758	.0739	11.9952	18.2579	16.5000
Regression	3.1477	130.2683	19.0000	4.8651	4.9696	.0582	.4983	.3000	.0734	.0728	11.9617	19.1969	16.5000

Table 6. Summary of Estimated Means

	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1	IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4
Alle Werte	11.7368	11.2333	.0571	.1595	.0537	.0500	.0544	4.1667	123.5316	32.8000	3.4000	3.5333	.0600	.0416	.0100	4.4010
Regression	11.7431	11.3960	.0584	.1656	.0540	.0500	.0566	3.9633	128.5497	32.8000	3.6367	3.3378	.0665	.0365	.0105	5.5301

Table 7. Summary of Estimated Means

	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3	IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5
Alle Werte	.05414	.08100	.07460	.09899	.08820	.03959	1.19149	.97585	4.45477	1.07476	1.76861
Regression	.05644	.07555	.06711	.09740	.08415	.03459	1.16505	.90669	4.37847	1.03174	1.62629

Table 8. Summary of Estimated Means

	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
Alle Werte	.	3.34957	.96874	.	.
Regression	.00000	3.34957	.95475	.00000	.00000

Table 9. Summary of Estimated Standard Deviations

	Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4
All Values	8.521	73.818	1.895	4.845	1.949	1.032	2.569	3.83279	1.283	.999
EM	8.521	73.818	1.895	4.845	1.949	1.032	2.569	3.83279	1.283	.999

Table10. Summary of Estimated Standard Deviations

	mmstot_V5	VLMT_Learning_V5	vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5
All Values	.992	10.653	3.586	3.566	6.318	8.883	14.231	69.924	11.946	5.953
EM	.992	10.653	3.586	3.566	6.318	7.279	14.231	69.924	11.946	5.953

Table 11. Summary of Estimated Standard Deviations

	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5	PTSS_10_Tot	PHQ_D_Somatic_Scale	PHQ_D_Depression_Scale	CRP_V1	CRP_V2	CRP_V3
All Values	5.019	1.888	1.849	9.090	7.216	4.080	3.893	3.96413	84.77728	.
EM	5.019	1.888	1.849	8.895	7.059	4.080	3.893	3.77858	77.07268	.00000

Table 12. Summary of Estimated Standard Deviations

	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4	PCT_V5	NSE_V1	NSE_V2	NSE_V3
All Values	6.16581	7.90538	.02047	.58627	.	.02293	.02893	4.84721	7.31341	.
EM	6.32813	7.49284	.01928	.60698	.00000	.02409	.02806	4.56753	6.81365	.00000

Table 13. Summary of Estimated Standard Deviations

	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1	IL_6_V2	IL_6_V3
All Values	3.01021	2.83777	.01927	.10860	.02290	.	.02617	3.29262	154.49703	.
EM	2.71212	2.68325	.01896	.10812	.02128	.00000	.02336	3.15073	140.71885	.00000

Table 14. Summary of Estimated Standard Deviations

	IL_6_V4	IL_6_V5	IL1_al-pha_V1	IL1_al-pha_V2	IL1_al-pha_V3	IL1_al-pha_V4	IL1_al-pha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
All Values	2.52433	2.54003	.17187	.09179	.01414	19.98934	.05414	.08100	.07460	.09899
EM	2.32412	2.23541	.16431	.08291	.01403	18.90672	.05644	.07555	.06711	.09740

Table 15. Summary of Estimated Standard Deviations

	IL1_beta_V4	IL1_beta_V6	TNF_al-pha_V1	TNF_al-pha_V2	TNF_al-pha_V3	TNF_al-pha_V4	TNF_al-pha_V5	LZ_V1	LZ_V2	LZ_V3
All Values	.08820	.03959	1.19149	.97585	4.45477	1.07476	1.76861	.	3.34957	.96874
EM	.08415	.03459	1.16505	.90669	4.37847	1.03174	1.62629	.00000	3.34957	.95475

Table16. Summary of Estimated Standard

Deviations

	LZ_V4	LZ_V5
All Values	.	.
EM	.00000	.00000

Table 17. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Second-ary_Edu_Yrs	Ter-tiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learn-ing_V5
wms4vw2tot_V6	t	2.6	-.8	1.9	-.7	-1.0	1.5	.1	-.4	1.5	-.2	.5	-2.0
	df	17.6	22.0	12.8	17.2	19.4	16.4	18.7	21.6	21.9	19.1	15.3	21.0
	P(2-tail)	13	13	13	13	13	13	13	13	13	13	13	13
	# Present	11	11	11	11	11	11	11	11	11	11	11	11
	# Missing	67.77	267.77	2.46	4.23	9.46	3.54	13.15	26.7915	24.92	29.00	29.23	37.85
	Mean(Pre-sent)	59.55	291.82	1.18	5.73	10.27	2.91	13.00	27.3509	24.18	29.09	29.00	45.82
CRP_V1	t	-2.3	.9	1.1	.5	.1	-1.4	-1.4	.2	-.2	-.5	.2	-.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Pre-sent)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
CRP_V2	t	.2	-1.0	-.8	-.4	-.6	.4	.2	-1.2	.5	.1	1.7	.1
	df	5.3	15.5	4.1	8.3	5.2	4.3	4.6	5.7	9.8	6.4	4.5	6.2
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	64.26	273.79	1.58	4.74	9.68	3.32	13.16	26.5237	24.63	29.05	29.37	41.63
	Mean(Pre-sent)	63.00	297.80	3.00	5.60	10.40	3.00	12.80	29.0400	24.40	29.00	28.20	41.00
CRP_V3	t	.	.	.	.	.	.	.	.	.	.	.	.
	df	.	.	.	.	.	.	.	.	.	.	.	.
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	23	23	23	23	23	23	23	23	23
	# Missing	70.00	330.00	10.00	1.00	10.00	3.00	11.00	31.6400	25.00	28.00	28.00	24.00
	Mean(Pre-sent)	63.74	276.57	1.52	5.09	9.83	3.26	13.17	26.8483	24.57	29.09	29.17	42.26
CRP_V4	t	-.1	.8	1.0	1.3	2.5	-.5	-.5	-1.4	-.5	-1.0	-.2	.7
	df	6.4	7.0	16.2	9.5	15.8	14.1	7.2	4.9	4.3	7.1	7.7	16.3
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	63.89	284.68	2.00	5.42	10.16	3.21	12.95	26.3605	24.47	28.95	29.11	42.00
	Mean(Pre-sent)	64.40	256.40	1.40	3.00	8.60	3.40	13.60	29.6600	25.00	29.40	29.20	39.60
CRP_V5	T	1.7	1.2	1.8	.5	-.4	1.7	-.1	.5	-.9	-2.1	-.7	-1.1
	df	6.8	10.3	20.1	11.8	7.3	6.1	7.1	13.8	5.7	10.3	11.1	14.8
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	65.94	288.00	2.11	5.17	9.72	3.50	13.06	27.2450	24.39	28.83	29.06	40.39
	Mean(Pre-sent)	58.17	251.17	1.17	4.17	10.17	2.50	13.17	26.4567	25.17	29.67	29.33	44.83
PCT_V1	t	-2.3	.9	1.1	.5	.1	-1.4	-1.4	.2	-.2	-.5	.2	-.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Pre-sent)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table18. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
wms4vw2tot_V6	t	-2.1	-1.9	-0.8		0.3	0.5	-0.9	-0.6	-0.5	-0.2	-1.2	-1.9
	df	21.1	21.3	22.0		14.5	20.0	15.2	18.3	21.6	22.0	21.9	11.1
	P(2-tail)	13	13	13	13	13	13	13	13	13	13	13	12
	# Present	11	11	11	0	11	11	11	11	11	11	11	11
	# Missing	5.31	6.08	31.31	27.92	46.31	123.08	42.08	20.23	10.69	6.92	5.46	3.08
	Mean(Present)	8.09	8.64	33.27		44.64	108.64	46.82	21.82	11.73	7.09	6.36	10.09
CRP_V1	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
CRP_V2	t	0.7	0.4	1.4		0.1	0.0	-0.2	-0.2	-1.0	0.3	1.1	-1.2
	df	11.0	9.3	7.4		4.9	5.8	6.4	4.6	7.5	7.4	5.5	4.6
	P(2-tail)	19	19	19	12	19	19	19	19	19	19	19	18
	# Present	5	5	5	1	5	5	5	5	5	5	5	5
	# Missing	6.79	7.37	33.00	27.67	45.68	116.84	44.00	20.74	10.68	7.05	6.11	4.78
	Mean(Present)	5.80	6.80	29.20	31.00	45.00	115.00	45.20	21.80	13.00	6.80	5.00	12.40
CRP_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	12	23	23	23	23	23	23	23	22
	# Missing	3.00	4.00	27.00	31.00	39.00	138.00	41.00	17.00	20.00	6.00	2.00	1.00
	Mean(Present)	6.74	7.39	32.43	27.67	45.83	115.52	44.39	21.13	10.78	7.04	6.04	6.68
CRP_V4	t	0.9	0.6	-0.3	-2.8	1.0	1.9	-0.7	-0.4	0.4	1.5	0.5	0.0
	df	10.8	9.6	7.4	4.0	10.0	20.3	16.0	8.0	4.6	7.4	11.5	6.0
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.84	7.42	32.00	26.36	46.68	123.89	43.63	20.74	11.47	7.26	5.95	6.44
	Mean(Present)	5.60	6.60	33.00	36.50	41.20	88.20	46.60	21.80	10.00	6.00	5.60	6.40
CRP_V5	T	-0.3	-0.6	-0.7		2.5	3.2	-2.0	-1.9	-0.3	0.0	-0.9	0.1
	df	15.3	13.9	9.2		10.5	21.9	8.0	12.9	6.2	7.0	7.6	9.1
	P(2-tail)	18	18	18	12	18	18	18	18	18	18	18	17
	# Present	6	6	6	1	6	6	6	6	6	6	6	6
	# Missing	6.50	7.06	31.67	27.42	49.00	131.89	41.44	19.89	10.94	7.00	5.67	6.59
	Mean(Present)	6.83	7.83	33.83	34.00	35.17	70.17	52.67	24.17	11.83	7.00	6.50	6.00
PCT_V1	t	-2.1	-1.9	-0.8		0.3	0.5	-0.9	-0.6	-0.5	-0.2	-1.2	-1.9
	df	21.1	21.3	22.0		14.5	20.0	15.2	18.3	21.6	22.0	21.9	11.1
	P(2-tail)	13	13	13	13	13	13	13	13	13	13	13	12
	# Present	11	11	11	0	11	11	11	11	11	11	11	11
	# Missing	5.31	6.08	31.31	27.92	46.31	123.08	42.08	20.23	10.69	6.92	5.46	3.08
	Mean(Present)	8.09	8.64	33.27		44.64	108.64	46.82	21.82	11.73	7.09	6.36	10.09

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 19. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_Somatic_Scale	PHQ_D_Depression_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
wms4vw2tot_V6	t	0.5	-1.9	-0.3	3.0	0.9		0.8	-0.1	0.4	1.0		0.8
	df	20.5	14.7	21.4	10.5	17.0		13.9	9.8	15.9	15.4		16.9
	P(2-tail)	13	13	13	11	12	1	11	12	11	12	1	11
	# Present	10	11	11	10	7	0	8	6	10	7	0	8
	# Missing	17.23	2.54	3.62	5.4364	133.625	019.0000	4.8000	5.1583	0.0609	0.7233	0.3000	0.0791
	Mean(Present)	15.80	5.64	4.18	1.2300	102.7000		2.6750	5.3667	0.0570	0.4971		0.0713
CRP_V1	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.847	119.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
CRP_V2	t	-1.2	-2.0	-0.2	2.0			0.0	0.3	0.6			-0.1
	df	6.1	4.5	7.3	18.4			8.0	9.2	3.8			3.9
	P(2-tail)	18	19	19	17	19	0	15	15	17	19	0	15
	# Present	5	5	5	4	0	1	4	3	4	0	1	4
	# Missing	15.67	2.84	3.79	3.8824	122.2316	0.0000	3.8867	5.3933	0.0606	0.6400	0.0000	0.0753
	Mean(Present)	20.00	8.20	4.20	1.5250		19.0000	3.9750	4.4000	0.0525		0.3000	0.0775
CRP_V3	t												
	df												
	P(2-tail)	1	1	1	1	0	1	1	1	1	0	1	1
	# Present	22	23	23	20	19	0	18	17	20	19	0	18
	# Missing	14.00	5.00	1.00	3.1000	0.0000	19.0000	2.6000	7.9000	0.0700	0.0000	0.3000	0.1100
	Mean(Present)	16.73	3.91	4.00	3.4500	122.2316		3.9778	5.0706	0.0585	0.6400		0.0739
CRP_V4	t	-0.2	1.0	0.6	-0.8	2.5				1.7	-0.3		
	df	5.6	9.1	7.6	3.1	6.7				14.3	3.4		
	P(2-tail)	18	19	19	17	15	1	19	17	17	15	1	19
	# Present	5	5	5	4	4	0	0	1	4	4	0	0
	# Missing	16.44	4.32	4.11	2.7941	141.166	719.0000	3.9053	5.5235	0.0612	0.6100	0.3000	0.0758
	Mean(Present)	17.20	2.60	3.00	6.1500	51.2250			0.2000	0.0500	0.7525		
CRP_V5	T	0.5	0.7	2.0	-0.4	2.0		-0.4		3.0	-0.5		1.5
	df	8.5	16.9	19.5	4.2	8.7		1.2		16.5	3.5		1.7
	P(2-tail)	17	18	18	16	15	1	17	18	16	15	1	17
	# Present	6	6	6	5	4	0	2	0	5	4	0	2
	# Missing	17.12	4.22	4.50	3.1000	136.720	019.0000	3.7235	5.2278	0.0638	0.5913	0.3000	0.0776
	Mean(Present)	15.17	3.17	2.00	4.5000	67.9000		5.4500		0.0440	0.8225		0.0600
PCT_V1	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 20. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
wms4vw2tot_V6	t	0.4	0.7	-1.3		-0.5	0.3	-1.1	-0.2	-1.0		0.3	2.1
	df	8.6	11.2	12.6		15.0	11.0	18.4	9.0	11.9		13.3	11.9
	P(2-tail)	12	11	12	1	11	12	11	12	11	1	12	11
	# Present	6	10	7	0	8	6	10	7	8	0	6	10
	# Missing	0.0758	12.7182	16.5667	16.5000	11.4273	11.3583	0.0527	0.1558	0.0491	0.0500	0.0558	5.4455
	Mean(Present)	0.0700	11.2000	21.1571		12.1625	10.9833	0.0620	0.1657	0.0600		0.0517	2.7600
CRP_V1	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
CRP_V2	t	-1.9	-0.1			0.6	0.2	-0.6		-0.7		-0.2	-0.9
	df	2.4	4.6			6.6	3.9	3.5		3.3		3.0	3.3
	P(2-tail)	15	17	19	0	15	15	17	19	15	0	15	17
	# Present	3	4	0	1	4	3	4	0	4	1	3	4
	# Missing	0.0673	11.9294	18.2579	0.0000	11.9067	11.2933	0.0553	0.1595	0.0507	0.0000	0.0540	3.6824
	Mean(Present)	0.1067	12.2750		16.5000	11.1000	10.9333	0.0650		0.0650	0.0500	0.0567	6.2250
CRP_V3	t												
	df												
	P(2-tail)	1	1	0	1	1	1	1	0	1	1	1	1
	# Present	17	20	19	0	18	17	20	19	18	0	17	20
	# Missing	0.1400	19.5000	0.0000	16.5000	10.9000	10.8000	0.0300	0.0000	0.0300	0.0500	0.0300	14.5000
	Mean(Present)	0.0700	11.6200	18.2579		11.7833	11.2588	0.0585	0.1595	0.0550		0.0559	3.6500
CRP_V4	t		0.1	-3.7				0.3	-1.3				-1.4
	df		14.1	12.1				5.1	3.6				3.9
	P(2-tail)	17	17	15	1	19	17	17	15	19	1	17	17
	# Present	1	4	4	0	0	1	4	4	0	0	1	4
	# Missing	0.0753	12.0294	16.3933	16.5000	11.7368	11.0529	0.0576	0.1380	0.0537	0.0500	0.0559	3.6235
	Mean(Present)	0.0500	11.8500	25.2500			14.3000	0.0550	0.2400			0.0300	6.4750
CRP_V5	T		0.5	-4.0		-0.1		-0.8	-1.4	-1.0			-0.7
	df		18.4	7.5		1.5		11.1	3.6	1.0			5.9
	P(2-tail)	18	16	15	1	17	18	16	15	17	1	18	16
	# Present	0	5	4	0	2	0	5	4	2	0	0	5
	# Missing	0.0739	12.2000	16.0533	16.5000	11.7118	11.2333	0.0556	0.1373	0.0500	0.0500	0.0544	3.8750
	Mean(Present)		11.3400	26.5250		11.9500		0.0620	0.2425	0.0850			5.1000
PCT_V1	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 21. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
wms4vw2tot_V6	t	1.0		0.8	0.9	1.7	0.6		-1.0	-1.5	0.8	-0.1	
	df	13.4		12.8	15.9	10.0	16.3		7.0	6.4	17.9	14.7	
	P(2-tail)	12	1	11	12	11	11	2	13	13	11	11	2
	# Present	7	0	8	6	10	8	0	8	6	10	8	0
	# Missing	144.2167	32.8000	3.7636	3.8333	0.1145	0.0518	0.0100	0.0454	0.0123	0.1273	0.1264	0.2500
	Mean(Present)	88.0714		2.9000	2.9333	0.0000	0.0275		11.4788	0.0600	0.0970	0.1288	
CRP_V1	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
CRP_V2	t			-0.2	-1.1	1.6	2.0		1.0	0.2	0.1	0.0	
	df			11.9	2.0	16.0	16.0		16.0	3.7	4.3	1.1	
	P(2-tail)	19	0	15	15	17	17	1	17	16	17	17	1
	# Present	0	1	4	3	4	2	1	4	3	4	2	1
	# Missing	123.5316	0.0000	3.3600	2.9800	0.0741	0.0465	0.0200	5.4341	0.0281	0.1141	0.1271	0.3200
	Mean(Present)		32.8000	3.5500	6.3000	0.0000	0.0000	0.0000	0.0100	0.0233	0.1075	0.1300	0.1800
CRP_V3	t												
	df												
	P(2-tail)	0	1	1	1	1	1	1	1	1	1	1	1
	# Present	19	0	18	17	20	18	1	20	18	20	18	1
	# Missing	0.0000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2300	0.0600	0.1800
	Mean(Present)	123.5316		3.3111	3.0118	0.0630	0.0439	0.0200	4.6210	0.0289	0.1070	0.1311	0.3200
CRP_V4	t	-1.1				1.6	2.0		1.0	1.1	-0.3	-2.6	
	df	3.1				16.0	15.0		18.0	6.9	4.2	2.6	
	P(2-tail)	15	1	19	17	17	16	1	19	17	17	16	1
	# Present	4	0	0	1	4	3	1	2	2	4	3	1
	# Missing	86.9267	32.8000	3.4000	3.5412	0.0741	0.0494	0.0000	4.8632	0.0294	0.1100	0.1094	0.1800
	Mean(Present)	260.8000			3.4000	0.0000	0.0000	0.0200	0.0100	0.0100	0.1250	0.2233	0.3200
CRP_V5	T	0.5		0.9		1.6	2.0		1.0		0.7	-1.2	
	df	13.8		3.7		15.0	15.0		17.0		6.5	2.8	
	P(2-tail)	15	1	17	18	16	16	1	18	18	16	16	1
	# Present	4	0	2	0	5	3	1	3	1	5	3	1
	# Missing	129.6467	32.8000	3.4882	3.5333	0.0788	0.0494	0.0000	5.1333	0.0278	0.1200	0.1188	0.1800
	Mean(Present)	100.6000		2.6500		0.0000	0.0000	0.0200	0.0067	0.0200	0.0900	0.1733	0.3200
PCT_V1	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 22. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
wms4vw2tot_V6	t	1.3	-2.7	1.5	1.2		0.4	1.6		0.2			
	df	16.4	2.3	15.2	16.1		19.0	16.5		21.5			
	P(2-tail)	13	12	11	11	2	13	13	0	13	2	0	0
	# Present	8	2	10	8	0	8	6	0	11	0	0	0
	# Missing	0.0862	0.0642	3.1673	2.9182	5.6700	2.9146	3.3392	0.0000	10.3685	9.5450	0.0000	0.0000
	Mean(Present)	0.0438	0.1150	2.4380	2.4150		2.7413	2.3000		10.0755			
CRP_V1	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
CRP_V2	t	0.5	-2.1	-1.5	-4.8		-2.3	-1.1		-1.3			
	df	6.6	11.4	4.0	15.0		3.7	2.0		5.2			
	P(2-tail)	17	12	17	17	1	17	16	0	19	1	0	0
	# Present	4	2	4	2	1	4	3	0	5	1	0	0
	# Missing	0.0735	0.0675	2.6100	2.5794	2.5200	2.5588	2.6306	0.0000	9.6868	8.8600	0.0000	0.0000
	Mean(Present)	0.0550	0.0950	3.7125	3.7850	8.8200	4.0800	5.0400		12.3140	10.2300		
CRP_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	0	1	1	0	0
	# Present	20	13	20	18	1	20	18	0	23	1	0	0
	# Missing	0.1100	0.0900	5.2700	3.8800	8.8200	5.7400	9.3500	0.0000	14.9100	10.2300	0.0000	0.0000
	Mean(Present)	0.0680	0.0700	2.6975	2.6411	2.5200	2.7040	2.6589		10.0309	8.8600		
CRP_V4	t	0.9		-0.8	-0.6		0.0	-0.3		1.0			
	df	1.8		3.5	2.1		1.2	9.5		8.0			
	P(2-tail)	19	13	17	16	1	19	17	0	19	1	0	0
	# Present	2	1	4	3	1	2	2	0	5	1	0	0
	# Missing	0.0737	0.0746	2.6776	2.5988	8.8200	2.8489	2.9918	0.0000	10.5253	10.2300	0.0000	0.0000
	Mean(Present)	0.0350	0.0300	3.4250	3.2800	2.5200	2.8450	3.1750		9.1280	8.8600		
CRP_V5	T	-0.4		0.4	1.7		-1.3			1.0			
	df	12.9		14.2	15.4		3.4			11.3			
	P(2-tail)	18	14	16	16	1	18	18	0	18	1	0	0
	# Present	3	0	5	3	1	3	1	0	6	1	0	0
	# Missing	0.0683	0.0714	2.8619	2.7875	8.8200	2.7517	2.9867	0.0000	10.5839	10.2300	0.0000	0.0000
	Mean(Present)	0.0800		2.6860	2.2733	2.5200	3.4300	3.4500		9.1850	8.8600		
PCT_V1	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 23. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5
PCT_V2	t	0.2	-1.0	-0.8	-0.4	-0.6	0.4	0.2	-1.2	0.5	0.1	1.7	0.1
	df	5.3	15.5	4.1	8.3	5.2	4.3	4.6	5.7	9.8	6.4	4.5	6.2
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	64.26	273.79	1.58	4.74	9.68	3.32	13.16	26.5237	24.63	29.05	29.37	41.63
	Mean(Present)	63.00	297.80	3.00	5.60	10.40	3.00	12.80	29.0400	24.40	29.00	28.20	41.00
PCT_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	23	23	23	23	23	23	23	23	23
	# Missing	70.00	330.00	10.00	1.00	10.00	3.00	11.00	31.6400	25.00	28.00	28.00	24.00
	Mean(Present)	63.74	276.57	1.52	5.09	9.83	3.26	13.17	26.8483	24.57	29.09	29.17	42.26
PCT_V4	t	-0.1	0.8	1.0	1.3	2.5	-0.5	-0.5	-1.4	-0.5	-1.0	-0.2	0.7
	df	6.4	7.0	16.2	9.5	15.8	14.1	7.2	4.9	4.3	7.1	7.7	16.3
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	63.89	284.68	2.00	5.42	10.16	3.21	12.95	26.3605	24.47	28.95	29.11	42.00
	Mean(Present)	64.40	256.40	1.40	3.00	8.60	3.40	13.60	29.6600	25.00	29.40	29.20	39.60
PCT_V5	t	1.7	1.2	1.8	0.5	-0.4	1.7	-0.1	0.5	-0.9	-2.1	-0.7	-1.1
	df	6.8	10.3	20.1	11.8	7.3	6.1	7.1	13.8	5.7	10.3	11.1	14.8
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	65.94	288.00	2.11	5.17	9.72	3.50	13.06	27.2450	24.39	28.83	29.06	40.39
	Mean(Present)	58.17	251.17	1.17	4.17	10.17	2.50	13.17	26.4567	25.17	29.67	29.33	44.83
NSE_V1	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Present)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
NSE_V2	T	0.2	-1.0	-0.8	-0.4	-0.6	0.4	0.2	-1.2	0.5	0.1	1.7	0.1
	df	5.3	15.5	4.1	8.3	5.2	4.3	4.6	5.7	9.8	6.4	4.5	6.2
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	64.26	273.79	1.58	4.74	9.68	3.32	13.16	26.5237	24.63	29.05	29.37	41.63
	Mean(Present)	63.00	297.80	3.00	5.60	10.40	3.00	12.80	29.0400	24.40	29.00	28.20	41.00
NSE_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	23	23	23	23	23	23	23	23	23
	# Missing	70.00	330.00	10.00	1.00	10.00	3.00	11.00	31.6400	25.00	28.00	28.00	24.00
	Mean(Present)	63.74	276.57	1.52	5.09	9.83	3.26	13.17	26.8483	24.57	29.09	29.17	42.26

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 24 Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
PCT_V2	t	7	0.4	1.4		0.1	0.0	-0.2	-0.2	-1.0	0.3	1.1	-1.2
	df	11.0	9.3	7.4		4.9	5.8	6.4	4.6	7.5	7.4	5.5	4.6
	P(2-tail)	19	19	19	12	19	19	19	19	19	19	19	18
	# Present	5	5	5	1	5	5	5	5	5	5	5	5
	# Missing	6.79	7.37	33.00	27.67	45.68	116.84	44.00	20.74	10.68	7.05	6.11	4.78
	Mean(Present)	5.80	6.80	29.20	31.00	45.00	115.00	45.20	21.80	13.00	6.80	5.00	12.40
PCT_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	12	23	23	23	23	23	23	23	22
	# Missing	3.00	4.00	27.00	31.00	39.00	138.00	41.00	17.00	20.00	6.00	2.00	1.00
	Mean(Present)	6.74	7.39	32.43	27.67	45.83	115.52	44.39	21.13	10.78	7.04	6.04	6.68
PCT_V4	t	0.9	0.6	-0.3	-2.8	1.0	1.9	-0.7	-0.4	0.4	1.5	0.5	0.0
	df	10.8	9.6	7.4	4.0	10.0	20.3	16.0	8.0	4.6	7.4	11.5	6.0
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.84	7.42	32.00	26.36	46.68	123.89	43.63	20.74	11.47	7.26	5.95	6.44
	Mean(Present)	5.60	6.60	33.00	36.50	41.20	88.20	46.60	21.80	10.00	6.00	5.60	6.40
PCT_V5	t	-0.3	-0.6	-0.7		2.5	3.2	-2.0	-1.9	-0.3	0.0	-0.9	0.1
	df	15.3	13.9	9.2		10.5	21.9	8.0	12.9	6.2	7.0	7.6	9.1
	P(2-tail)	18	18	18	12	18	18	18	18	18	18	18	17
	# Present	6	6	6	1	6	6	6	6	6	6	6	6
	# Missing	6.50	7.06	31.67	27.42	49.00	131.89	41.44	19.89	10.94	7.00	5.67	6.59
	Mean(Present)	6.83	7.83	33.83	34.00	35.17	70.17	52.67	24.17	11.83	7.00	6.50	6.00
NSE_V1	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
NSE_V2	T	0.7	0.4	1.4		0.1	0.0	-0.2	-0.2	-1.0	0.3	1.1	-1.2
	df	11.0	9.3	7.4		4.9	5.8	6.4	4.6	7.5	7.4	5.5	4.6
	P(2-tail)	19	19	19	12	19	19	19	19	19	19	19	18
	# Present	5	5	5	1	5	5	5	5	5	5	5	5
	# Missing	6.79	7.37	33.00	27.67	45.68	116.84	44.00	20.74	10.68	7.05	6.11	4.78
	Mean(Present)	5.80	6.80	29.20	31.00	45.00	115.00	45.20	21.80	13.00	6.80	5.00	12.40
NSE_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	12	23	23	23	23	23	23	23	22
	# Missing	3.00	4.00	27.00	31.00	39.00	138.00	41.00	17.00	20.00	6.00	2.00	1.00
	Mean(Present)	6.74	7.39	32.43	27.67	45.83	115.52	44.39	21.13	10.78	7.04	6.04	6.68

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 25 Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-sion_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
PCT_V2	t	-1.2	-2.0	-0.2	2.0			0.0	0.3	0.6			-0.1
	df	6.1	4.5	7.3	18.4			8.0	9.2	3.8			3.9
	P(2-tail)	18	19	19	17	19	0	15	15	17	19	0	15
	# Present	5	5	5	4	0	1	4	3	4	0	1	4
	# Missing	15.67	2.84	3.79	3.8824	122.2316	0.0000	3.8867	5.3933	0.0606	0.6400	0.0000	0.0753
	Mean(Present)	20.00	8.20	4.20	1.5250		19.0000	3.9750	4.4000	0.0525		0.3000	0.0775
PCT_V3	t												
	df												
	P(2-tail)	1	1	1	1	0	1	1	1	1	0	1	1
	# Present	22	23	23	20	19	0	18	17	20	19	0	18
	# Missing	14.00	5.00	1.00	3.1000	0.0000	19.0000	2.6000	7.9000	0.0700	0.0000	0.3000	0.1100
	Mean(Present)	16.73	3.91	4.00	3.4500	122.2316		3.9778	5.0706	0.0585	0.6400		0.0739
PCT_V4	t	-0.2	1.0	0.6	-0.8	2.5				1.7	-0.3		
	df	5.6	9.1	7.6	3.1	6.7				14.3	3.4		
	P(2-tail)	18	19	19	17	15	1	19	17	17	15	1	19
	# Present	5	5	5	4	4	0	0	1	4	4	0	0
	# Missing	16.44	4.32	4.11	2.7941	141.1667	19.0000	3.9053	5.5235	0.0612	0.6100	0.3000	0.0758
	Mean(Present)	17.20	2.60	3.00	6.1500	51.2250			0.2000	0.0500	0.7525		
PCT_V5	t	0.5	0.7	2.0	-0.4	2.0		-0.4		3.0	-0.5		1.5
	df	8.5	16.9	19.5	4.2	8.7		1.2		16.5	3.5		1.7
	P(2-tail)	17	18	18	16	15	1	17	18	16	15	1	17
	# Present	6	6	6	5	4	0	2	0	5	4	0	2
	# Missing	17.12	4.22	4.50	3.1000	136.7200	19.0000	3.7235	5.2278	0.0638	0.5913	0.3000	0.0776
	Mean(Present)	15.17	3.17	2.00	4.5000	67.9000		5.4500		0.0440	0.8225		0.0600
NSE_V1	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
NSE_V2	T	-1.2	-2.0	-0.2	2.0			0.0	0.3	0.6			-0.1
	df	6.1	4.5	7.3	18.4			8.0	9.2	3.8			3.9
	P(2-tail)	18	19	19	17	19	0	15	15	17	19	0	15
	# Present	5	5	5	4	0	1	4	3	4	0	1	4
	# Missing	15.67	2.84	3.79	3.8824	122.2316	0.0000	3.8867	5.3933	0.0606	0.6400	0.0000	0.0753
	Mean(Present)	20.00	8.20	4.20	1.5250		19.0000	3.9750	4.4000	0.0525		0.3000	0.0775
NSE_V3	t												
	df												
	P(2-tail)	1	1	1	1	0	1	1	1	1	0	1	1
	# Present	22	23	23	20	19	0	18	17	20	19	0	18
	# Missing	14.00	5.00	1.00	3.1000	0.0000	19.0000	2.6000	7.9000	0.0700	0.0000	0.3000	0.1100
	Mean(Present)	16.73	3.91	4.00	3.4500	122.2316		3.9778	5.0706	0.0585	0.6400		0.0739

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 26 Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
PCT_V2	t	-1.9	-0.1			0.6	0.2	-0.6		-0.7		-0.2	-0.9
	df	2.4	4.6			6.6	3.9	3.5		3.3		3.0	3.3
	P(2-tail)	15	17	19	0	15	15	17	19	15	0	15	17
	# Present	3	4	0	1	4	3	4	0	4	1	3	4
	# Missing	0.0673	11.9294	18.2579	0.0000	11.9067	11.2933	0.0553	0.1595	0.0507	0.0000	0.0540	3.6824
	Mean(Present)	0.1067	12.2750		16.5000	11.1000	10.9333	0.0650		0.0650	0.0500	0.0567	6.2250
PCT_V3	t												
	df												
	P(2-tail)	1	1	0	1	1	1	1	0	1	1	1	1
	# Present	17	20	19	0	18	17	20	19	18	0	17	20
	# Missing	0.1400	19.5000	0.0000	16.5000	10.9000	10.8000	0.0300	0.0000	0.0300	0.0500	0.0300	14.5000
	Mean(Present)	0.0700	11.6200	18.2579		11.7833	11.2588	0.0585	0.1595	0.0550		0.0559	3.6500
PCT_V4	t		0.1	-3.7				0.3	-1.3				-1.4
	df		14.1	12.1				5.1	3.6				3.9
	P(2-tail)	17	17	15	1	19	17	17	15	19	1	17	17
	# Present	1	4	4	0	0	1	4	4	0	0	1	4
	# Missing	0.0753	12.0294	16.3933	16.5000	11.7368	11.0529	0.0576	0.1380	0.0537	0.0500	0.0559	3.6235
	Mean(Present)	0.0500	11.8500	25.2500			14.3000	0.0550	0.2400			0.0300	6.4750
PCT_V5	t		0.5	-4.0		-0.1		-0.8	-1.4	-1.0			-0.7
	df		18.4	7.5		1.5		11.1	3.6	1.0			5.9
	P(2-tail)	18	16	15	1	17	18	16	15	17	1	18	16
	# Present	0	5	4	0	2	0	5	4	2	0	0	5
	# Missing	0.0739	12.2000	16.0533	16.5000	11.7118	11.2333	0.0556	0.1373	0.0500	0.0500	0.0544	3.8750
	Mean(Present)		11.3400	26.5250		11.9500		0.0620	0.2425	0.0850			5.1000
NSE_V1	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
NSE_V2	T	-1.9	-0.1			0.6	0.2	-0.6		-0.7		-0.2	-0.9
	df	2.4	4.6			6.6	3.9	3.5		3.3		3.0	3.3
	P(2-tail)	15	17	19	0	15	15	17	19	15	0	15	17
	# Present	3	4	0	1	4	3	4	0	4	1	3	4
	# Missing	0.0673	11.9294	18.2579	0.0000	11.9067	11.2933	0.0553	0.1595	0.0507	0.0000	0.0540	3.6824
	Mean(Present)	0.1067	12.2750		16.5000	11.1000	10.9333	0.0650		0.0650	0.0500	0.0567	6.2250
NSE_V3	t												
	df												
	P(2-tail)	1	1	0	1	1	1	1	0	1	1	1	1
	# Present	17	20	19	0	18	17	20	19	18	0	17	20
	# Missing	0.1400	19.5000	0.0000	16.5000	10.9000	10.8000	0.0300	0.0000	0.0300	0.0500	0.0300	14.5000
	Mean(Present)	0.0700	11.6200	18.2579		11.7833	11.2588	0.0585	0.1595	0.0550		0.0559	3.6500

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 27. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
PCT_V2	t			-0.2	-1.1	1.6	2.0		1.0	0.2	0.1	0.0	
	df			11.9	2.0	16.0	16.0		16.0	3.7	4.3	1.1	
	P(2-tail)	19	0	15	15	17	17	1	17	16	17	17	1
	# Present	0	1	4	3	4	2	1	4	3	4	2	1
	# Missing	123.5316	0.0000	3.3600	2.9800	0.0741	0.0465	0.0200	5.4341	0.0281	0.1141	0.1271	0.3200
	Mean(Present)		32.8000	3.5500	6.3000	0.0000	0.0000	0.0000	0.0100	0.0233	0.1075	0.1300	0.1800
PCT_V3	t												
	df												
	P(2-tail)	0	1	1	1	1	1	1	1	1	1	1	1
	# Present	19	0	18	17	20	18	1	20	18	20	18	1
	# Missing	0.0000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2300	0.0600	0.1800
	Mean(Present)	123.5316		3.3111	3.0118	0.0630	0.0439	0.0200	4.6210	0.0289	0.1070	0.1311	0.3200
PCT_V4	t	-1.1				1.6	2.0		1.0	1.1	-0.3	-2.6	
	df	3.1				16.0	15.0		18.0	6.9	4.2	2.6	
	P(2-tail)	15	1	19	17	17	16	1	19	17	17	16	1
	# Present	4	0	0	1	4	3	1	2	2	4	3	1
	# Missing	86.9267	32.8000	3.4000	3.5412	0.0741	0.0494	0.0000	4.8632	0.0294	0.1100	0.1094	0.1800
	Mean(Present)	260.8000			3.4000	0.0000	0.0000	0.0200	0.0100	0.0100	0.1250	0.2233	0.3200
PCT_V5	t	0.5		0.9		1.6	2.0		1.0		0.7	-1.2	
	df	13.8		3.7		15.0	15.0		17.0		6.5	2.8	
	P(2-tail)	15	1	17	18	16	16	1	18	18	16	16	1
	# Present	4	0	2	0	5	3	1	3	1	5	3	1
	# Missing	129.6467	32.8000	3.4882	3.5333	0.0788	0.0494	0.0000	5.1333	0.0278	0.1200	0.1188	0.1800
	Mean(Present)	100.6000		2.6500		0.0000	0.0000	0.0200	0.0067	0.0200	0.0900	0.1733	0.3200
NSE_V1	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
NSE_V2	T			-0.2	-1.1	1.6	2.0		1.0	0.2	0.1	0.0	
	df			11.9	2.0	16.0	16.0		16.0	3.7	4.3	1.1	
	P(2-tail)	19	0	15	15	17	17	1	17	16	17	17	1
	# Present	0	1	4	3	4	2	1	4	3	4	2	1
	# Missing	123.5316	0.0000	3.3600	2.9800	0.0741	0.0465	0.0200	5.4341	0.0281	0.1141	0.1271	0.3200
	Mean(Present)		32.8000	3.5500	6.3000	0.0000	0.0000	0.0000	0.0100	0.0233	0.1075	0.1300	0.1800
NSE_V3	t												
	df												
	P(2-tail)	0	1	1	1	1	1	1	1	1	1	1	1
	# Present	19	0	18	17	20	18	1	20	18	20	18	1
	# Missing	0.0000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2300	0.0600	0.1800
	Mean(Present)	123.5316		3.3111	3.0118	0.0630	0.0439	0.0200	4.6210	0.0289	0.1070	0.1311	0.3200

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 28. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
PCT_V2	t	0.5	-2.1	-1.5	-4.8		-2.3	-1.1		-1.3			
	df	6.6	11.4	4.0	15.0		3.7	2.0		5.2			
	P(2-tail)	17	12	17	17	1	17	16	0	19	1	0	0
	# Present	4	2	4	2	1	4	3	0	5	1	0	0
	# Missing	0.0735	0.0675	2.6100	2.5794	2.5200	2.5588	2.6306	0.0000	9.6868	8.8600	0.0000	0.0000
	Mean(Present)	0.0550	0.0950	3.7125	3.7850	8.8200	4.0800	5.0400		12.3140	10.2300		
PCT_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	0	1	1	0	0
	# Present	20	13	20	18	1	20	18	0	23	1	0	0
	# Missing	0.1100	0.0900	5.2700	3.8800	8.8200	5.7400	9.3500	0.0000	14.9100	10.2300	0.0000	0.0000
	Mean(Present)	0.0680	0.0700	2.6975	2.6411	2.5200	2.7040	2.6589		10.0309	8.8600		
PCT_V4	t	0.9		-0.8	-0.6		0.0	-0.3		1.0			
	df	1.8		3.5	2.1		1.2	9.5		8.0			
	P(2-tail)	19	13	17	16	1	19	17	0	19	1	0	0
	# Present	2	1	4	3	1	2	2	0	5	1	0	0
	# Missing	0.0737	0.0746	2.6776	2.5988	8.8200	2.8489	2.9918	0.0000	10.5253	10.2300	0.0000	0.0000
	Mean(Present)	0.0350	0.0300	3.4250	3.2800	2.5200	2.8450	3.1750		9.1280	8.8600		
PCT_V5	t	-0.4		0.4	1.7		-1.3			1.0			
	df	12.9		14.2	15.4		3.4			11.3			
	P(2-tail)	18	14	16	16	1	18	18	0	18	1	0	0
	# Present	3	0	5	3	1	3	1	0	6	1	0	0
	# Missing	0.0683	0.0714	2.8619	2.7875	8.8200	2.7517	2.9867	0.0000	10.5839	10.2300	0.0000	0.0000
	Mean(Present)	0.0800		2.6860	2.2733	2.5200	3.4300	3.4500		9.1850	8.8600		
NSE_V1	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
NSE_V2	T	0.5	-2.1	-1.5	-4.8		-2.3	-1.1		-1.3			
	df	6.6	11.4	4.0	15.0		3.7	2.0		5.2			
	P(2-tail)	17	12	17	17	1	17	16	0	19	1	0	0
	# Present	4	2	4	2	1	4	3	0	5	1	0	0
	# Missing	0.0735	0.0675	2.6100	2.5794	2.5200	2.5588	2.6306	0.0000	9.6868	8.8600	0.0000	0.0000
	Mean(Present)	0.0550	0.0950	3.7125	3.7850	8.8200	4.0800	5.0400		12.3140	10.2300		
NSE_V3	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	0	1	1	0	0
	# Present	20	13	20	18	1	20	18	0	23	1	0	0
	# Missing	0.1100	0.0900	5.2700	3.8800	8.8200	5.7400	9.3500	0.0000	14.9100	10.2300	0.0000	0.0000
	Mean(Present)	0.0680	0.0700	2.6975	2.6411	2.5200	2.7040	2.6589		10.0309	8.8600		

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 29. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Second-ary_Edu_Yrs	Ter-tiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learn-ing_V5
NSE_V4	t	1.7	1.2	1.8	0.5	-0.4	1.7	-0.1	0.5	-0.9	-2.1	-0.7	-1.1
	df	6.8	10.3	20.1	11.8	7.3	6.1	7.1	13.8	5.7	10.3	11.1	14.8
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	65.94	288.00	2.11	5.17	9.72	3.50	13.06	27.2450	24.39	28.83	29.06	40.39
	Mean(Pre-sent)	58.17	251.17	1.17	4.17	10.17	2.50	13.17	26.4567	25.17	29.67	29.33	44.83
NSE_V5	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Pre-sent)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
S100_V1	t	0.2	-1.0	-0.8	-0.4	-0.6	0.4	0.2	-1.2	0.5	0.1	1.7	0.1
	df	5.3	15.5	4.1	8.3	5.2	4.3	4.6	5.7	9.8	6.4	4.5	6.2
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	64.26	273.79	1.58	4.74	9.68	3.32	13.16	26.5237	24.63	29.05	29.37	41.63
	Mean(Pre-sent)	63.00	297.80	3.00	5.60	10.40	3.00	12.80	29.0400	24.40	29.00	28.20	41.00
S100_V2	t	-0.1	0.8	1.0	1.3	2.5	-0.5	-0.5	-1.4	-0.5	-1.0	-0.2	0.7
	df	6.4	7.0	16.2	9.5	15.8	14.1	7.2	4.9	4.3	7.1	7.7	16.3
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	63.89	284.68	2.00	5.42	10.16	3.21	12.95	26.3605	24.47	28.95	29.11	42.00
	Mean(Pre-sent)	64.40	256.40	1.40	3.00	8.60	3.40	13.60	29.6600	25.00	29.40	29.20	39.60
S100_V4	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	23	23	23	23	23	23	23	23	23
	# Missing	70.00	330.00	10.00	1.00	10.00	3.00	11.00	31.6400	25.00	28.00	28.00	24.00
	Mean(Pre-sent)	63.74	276.57	1.52	5.09	9.83	3.26	13.17	26.8483	24.57	29.09	29.17	42.26
S100_V3	T	1.7	1.2	1.8	0.5	-0.4	1.7	-0.1	0.5	-0.9	-2.1	-0.7	-1.1
	df	6.8	10.3	20.1	11.8	7.3	6.1	7.1	13.8	5.7	10.3	11.1	14.8
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	65.94	288.00	2.11	5.17	9.72	3.50	13.06	27.2450	24.39	28.83	29.06	40.39
	Mean(Pre-sent)	58.17	251.17	1.17	4.17	10.17	2.50	13.17	26.4567	25.17	29.67	29.33	44.83
S100_V5	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Pre-sent)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 30. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
NSE_V4	t	-0.3	-0.6	-0.7		2.5	3.2	-2.0	-1.9	-0.3	0.0	-0.9	0.1
	df	15.3	13.9	9.2		10.5	21.9	8.0	12.9	6.2	7.0	7.6	9.1
	P(2-tail)	18	18	18	12	18	18	18	18	18	18	18	17
	# Present	6	6	6	1	6	6	6	6	6	6	6	6
	# Missing	6.50	7.06	31.67	27.42	49.00	131.89	41.44	19.89	10.94	7.00	5.67	6.59
	Mean(Present)	6.83	7.83	33.83	34.00	35.17	70.17	52.67	24.17	11.83	7.00	6.50	6.00
NSE_V5	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
S100_V1	t	0.7	0.4	1.4		0.1	0.0	-0.2	-0.2	-1.0	0.3	1.1	-1.2
	df	11.0	9.3	7.4		4.9	5.8	6.4	4.6	7.5	7.4	5.5	4.6
	P(2-tail)	19	19	19	12	19	19	19	19	19	19	19	18
	# Present	5	5	5	1	5	5	5	5	5	5	5	5
	# Missing	6.79	7.37	33.00	27.67	45.68	116.84	44.00	20.74	10.68	7.05	6.11	4.78
	Mean(Present)	5.80	6.80	29.20	31.00	45.00	115.00	45.20	21.80	13.00	6.80	5.00	12.40
S100_V2	t	0.9	0.6	-0.3	-2.8	1.0	1.9	-0.7	-0.4	0.4	1.5	0.5	0.0
	df	10.8	9.6	7.4	4.0	10.0	20.3	16.0	8.0	4.6	7.4	11.5	6.0
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.84	7.42	32.00	26.36	46.68	123.89	43.63	20.74	11.47	7.26	5.95	6.44
	Mean(Present)	5.60	6.60	33.00	36.50	41.20	88.20	46.60	21.80	10.00	6.00	5.60	6.40
S100_V4	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	12	23	23	23	23	23	23	23	22
	# Missing	3.00	4.00	27.00	31.00	39.00	138.00	41.00	17.00	20.00	6.00	2.00	1.00
	Mean(Present)	6.74	7.39	32.43	27.67	45.83	115.52	44.39	21.13	10.78	7.04	6.04	6.68
S100_V3	T	-0.3	-0.6	-0.7		2.5	3.2	-2.0	-1.9	-0.3	0.0	-0.9	0.1
	df	15.3	13.9	9.2		10.5	21.9	8.0	12.9	6.2	7.0	7.6	9.1
	P(2-tail)	18	18	18	12	18	18	18	18	18	18	18	17
	# Present	6	6	6	1	6	6	6	6	6	6	6	6
	# Missing	6.50	7.06	31.67	27.42	49.00	131.89	41.44	19.89	10.94	7.00	5.67	6.59
	Mean(Present)	6.83	7.83	33.83	34.00	35.17	70.17	52.67	24.17	11.83	7.00	6.50	6.00
S100_V5	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 31. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-sion_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
NSE_V4	t	0.5	0.7	2.0	-0.4	2.0		-0.4		3.0	-0.5		1.5
	df	8.5	16.9	19.5	4.2	8.7		1.2		16.5	3.5		1.7
	P(2-tail)	17	18	18	16	15	1	17	18	16	15	1	17
	# Present	6	6	6	5	4	0	2	0	5	4	0	2
	# Missing	17.12	4.22	4.50	3.1000	136.7200	19.0000	3.7235	5.2278	0.0638	0.5913	0.3000	0.0776
	Mean(Present)	15.17	3.17	2.00	4.5000	67.9000		5.4500		0.0440	0.8225		0.0600
NSE_V5	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
S100_V1	t	-1.2	-2.0	-0.2	2.0			0.0	0.3	0.6			-0.1
	df	6.1	4.5	7.3	18.4			8.0	9.2	3.8			3.9
	P(2-tail)	18	19	19	17	19	0	15	15	17	19	0	15
	# Present	5	5	5	4	0	1	4	3	4	0	1	4
	# Missing	15.67	2.84	3.79	3.8824	122.2316	0.0000	3.8867	5.3933	0.0606	0.6400	0.0000	0.0753
	Mean(Present)	20.00	8.20	4.20	1.5250		19.0000	3.9750	4.4000	0.0525		0.3000	0.0775
S100_V2	t	-0.2	1.0	0.6	-0.8	2.5				1.7	-0.3		
	df	5.6	9.1	7.6	3.1	6.7				14.3	3.4		
	P(2-tail)	18	19	19	17	15	1	19	17	17	15	1	19
	# Present	5	5	5	4	4	0	0	1	4	4	0	0
	# Missing	16.44	4.32	4.11	2.7941	141.1667	19.0000	3.9053	5.5235	0.0612	0.6100	0.3000	0.0758
	Mean(Present)	17.20	2.60	3.00	6.1500	51.2250			0.2000	0.0500	0.7525		
S100_V4	t												
	df												
	P(2-tail)	1	1	1	1	0	1	1	1	1	0	1	1
	# Present	22	23	23	20	19	0	18	17	20	19	0	18
	# Missing	14.00	5.00	1.00	3.1000	0.0000	19.0000	2.6000	7.9000	0.0700	0.0000	0.3000	0.1100
	Mean(Present)	16.73	3.91	4.00	3.4500	122.2316		3.9778	5.0706	0.0585	0.6400		0.0739
S100_V3	T	0.5	0.7	2.0	-0.4	2.0		-0.4		3.0	-0.5		1.5
	df	8.5	16.9	19.5	4.2	8.7		1.2		16.5	3.5		1.7
	P(2-tail)	17	18	18	16	15	1	17	18	16	15	1	17
	# Present	6	6	6	5	4	0	2	0	5	4	0	2
	# Missing	17.12	4.22	4.50	3.1000	136.7200	19.0000	3.7235	5.2278	0.0638	0.5913	0.3000	0.0776
	Mean(Present)	15.17	3.17	2.00	4.5000	67.9000		5.4500		0.0440	0.8225		0.0600
S100_V5	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table32. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
NSE_V4	t		0.5	-4.0		-0.1		-0.8	-1.4	-1.0			-0.7
	df		18.4	7.5		1.5		11.1	3.6	1.0			5.9
	P(2-tail)	18	16	15	1	17	18	16	15	17	1	18	16
	# Present	0	5	4	0	2	0	5	4	2	0	0	5
	# Missing	0.0739	12.2000	16.0533	16.5000	11.7118	11.2333	0.0556	0.1373	0.0500	0.0500	0.0544	3.8750
	Mean(Present)		11.3400	26.5250		11.9500		0.0620	0.2425	0.0850			5.1000
NSE_V5	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
S100_V1	t	-1.9	-0.1			0.6	0.2	-0.6		-0.7		-0.2	-0.9
	df	2.4	4.6			6.6	3.9	3.5		3.3		3.0	3.3
	P(2-tail)	15	17	19	0	15	15	17	19	15	0	15	17
	# Present	3	4	0	1	4	3	4	0	4	1	3	4
	# Missing	0.0673	11.9294	18.2579	0.0000	11.9067	11.2933	0.0553	0.1595	0.0507	0.0000	0.0540	3.6824
	Mean(Present)	0.1067	12.2750		16.5000	11.1000	10.9333	0.0650		0.0650	0.0500	0.0567	6.2250
S100_V2	t		0.1	-3.7				0.3	-1.3				-1.4
	df		14.1	12.1				5.1	3.6				3.9
	P(2-tail)	17	17	15	1	19	17	17	15	19	1	17	17
	# Present	1	4	4	0	0	1	4	4	0	0	1	4
	# Missing	0.0753	12.0294	16.3933	16.5000	11.7368	11.0529	0.0576	0.1380	0.0537	0.0500	0.0559	3.6235
	Mean(Present)	0.0500	11.8500	25.2500			14.3000	0.0550	0.2400			0.0300	6.4750
S100_V4	t												
	df												
	P(2-tail)	1	1	0	1	1	1	1	0	1	1	1	1
	# Present	17	20	19	0	18	17	20	19	18	0	17	20
	# Missing	0.1400	19.5000	0.0000	16.5000	10.9000	10.8000	0.0300	0.0000	0.0300	0.0500	0.0300	14.5000
	Mean(Present)	0.0700	11.6200	18.2579		11.7833	11.2588	0.0585	0.1595	0.0550		0.0559	3.6500
S100_V3	T		0.5	-4.0		-0.1		-0.8	-1.4	-1.0			-0.7
	df		18.4	7.5		1.5		11.1	3.6	1.0			5.9
	P(2-tail)	18	16	15	1	17	18	16	15	17	1	18	16
	# Present	0	5	4	0	2	0	5	4	2	0	0	5
	# Missing	0.0739	12.2000	16.0533	16.5000	11.7118	11.2333	0.0556	0.1373	0.0500	0.0500	0.0544	3.8750
	Mean(Present)		11.3400	26.5250		11.9500		0.0620	0.2425	0.0850			5.1000
S100_V5	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 33. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
NSE_V4	t	0.5		0.9		1.6	2.0		1.0		0.7	-1.2	
	df	13.8		3.7		15.0	15.0		17.0		6.5	2.8	
	P(2-tail)	15	1	17	18	16	16	1	18	18	16	16	1
	# Present	4	0	2	0	5	3	1	3	1	5	3	1
	# Missing	129.6467	32.8000	3.4882	3.5333	0.0788	0.0494	0.0000	5.1333	0.0278	0.1200	0.1188	0.1800
	Mean(Present)	100.6000		2.6500		0.0000	0.0000	0.0200	0.0067	0.0200	0.0900	0.1733	0.3200
NSE_V5	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
S100_V1	t			-0.2	-1.1	1.6	2.0		1.0	0.2	0.1	0.0	
	df			11.9	2.0	16.0	16.0		16.0	3.7	4.3	1.1	
	P(2-tail)	19	0	15	15	17	17	1	17	16	17	17	1
	# Present	0	1	4	3	4	2	1	4	3	4	2	1
	# Missing	123.5316	0.0000	3.3600	2.9800	0.0741	0.0465	0.0200	5.4341	0.0281	0.1141	0.1271	0.3200
	Mean(Present)		32.8000	3.5500	6.3000	0.0000	0.0000	0.0000	0.0100	0.0233	0.1075	0.1300	0.1800
S100_V2	t	-1.1				1.6	2.0		1.0	1.1	-0.3	-2.6	
	df	3.1				16.0	15.0		18.0	6.9	4.2	2.6	
	P(2-tail)	15	1	19	17	17	16	1	19	17	17	16	1
	# Present	4	0	0	1	4	3	1	2	2	4	3	1
	# Missing	86.9267	32.8000	3.4000	3.5412	0.0741	0.0494	0.0000	4.8632	0.0294	0.1100	0.1094	0.1800
	Mean(Present)	260.8000			3.4000	0.0000	0.0000	0.0200	0.0100	0.0100	0.1250	0.2233	0.3200
S100_V4	t												
	df												
	P(2-tail)	0	1	1	1	1	1	1	1	1	1	1	1
	# Present	19	0	18	17	20	18	1	20	18	20	18	1
	# Missing	0.0000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2300	0.0600	0.1800
	Mean(Present)	123.5316		3.3111	3.0118	0.0630	0.0439	0.0200	4.6210	0.0289	0.1070	0.1311	0.3200
S100_V3	T	0.5		0.9		1.6	2.0		1.0		0.7	-1.2	
	df	13.8		3.7		15.0	15.0		17.0		6.5	2.8	
	P(2-tail)	15	1	17	18	16	16	1	18	18	16	16	1
	# Present	4	0	2	0	5	3	1	3	1	5	3	1
	# Missing	129.6467	32.8000	3.4882	3.5333	0.0788	0.0494	0.0000	5.1333	0.0278	0.1200	0.1188	0.1800
	Mean(Present)	100.6000		2.6500		0.0000	0.0000	0.0200	0.0067	0.0200	0.0900	0.1733	0.3200
S100_V5	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 34. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
NSE_V4	t	-0.4		0.4	1.7		-1.3			1.0			
	df	12.9		14.2	15.4		3.4			11.3			
	P(2-tail)	18	14	16	16	1	18	18	0	18	1	0	0
	# Present	3	0	5	3	1	3	1	0	6	1	0	0
	# Missing	0.0683	0.0714	2.8619	2.7875	8.8200	2.7517	2.9867	0.0000	10.5839	10.2300	0.0000	0.0000
	Mean(Present)	0.0800		2.6860	2.2733	2.5200	3.4300	3.4500		9.1850	8.8600		
NSE_V5	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
S100_V1	t	0.5	-2.1	-1.5	-4.8		-2.3	-1.1		-1.3			
	df	6.6	11.4	4.0	15.0		3.7	2.0		5.2			
	P(2-tail)	17	12	17	17	1	17	16	0	19	1	0	0
	# Present	4	2	4	2	1	4	3	0	5	1	0	0
	# Missing	0.0735	0.0675	2.6100	2.5794	2.5200	2.5588	2.6306	0.0000	9.6868	8.8600	0.0000	0.0000
	Mean(Present)	0.0550	0.0950	3.7125	3.7850	8.8200	4.0800	5.0400		12.3140	10.2300		
S100_V2	t	0.9		-0.8	-0.6		0.0	-0.3		1.0			
	df	1.8		3.5	2.1		1.2	9.5		8.0			
	P(2-tail)	19	13	17	16	1	19	17	0	19	1	0	0
	# Present	2	1	4	3	1	2	2	0	5	1	0	0
	# Missing	0.0737	0.0746	2.6776	2.5988	8.8200	2.8489	2.9918	0.0000	10.5253	10.2300	0.0000	0.0000
	Mean(Present)	0.0350	0.0300	3.4250	3.2800	2.5200	2.8450	3.1750		9.1280	8.8600		
S100_V4	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	0	1	1	0	0
	# Present	20	13	20	18	1	20	18	0	23	1	0	0
	# Missing	0.1100	0.0900	5.2700	3.8800	8.8200	5.7400	9.3500	0.0000	14.9100	10.2300	0.0000	0.0000
	Mean(Present)	0.0680	0.0700	2.6975	2.6411	2.5200	2.7040	2.6589		10.0309	8.8600		
S100_V3	T	-0.4		0.4	1.7		-1.3			1.0			
	df	12.9		14.2	15.4		3.4			11.3			
	P(2-tail)	18	14	16	16	1	18	18	0	18	1	0	0
	# Present	3	0	5	3	1	3	1	0	6	1	0	0
	# Missing	0.0683	0.0714	2.8619	2.7875	8.8200	2.7517	2.9867	0.0000	10.5839	10.2300	0.0000	0.0000
	Mean(Present)	0.0800		2.6860	2.2733	2.5200	3.4300	3.4500		9.1850	8.8600		
S100_V5	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 35. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5
IL_6_V1	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	23	23	23	23	23	23	23	23	23
	# Missing	70.00	330.00	10.00	1.00	10.00	3.00	11.00	31.6400	25.00	28.00	28.00	24.00
	Mean(Present)	63.74	276.57	1.52	5.09	9.83	3.26	13.17	26.8483	24.57	29.09	29.17	42.26
IL_6_V2	t	-0.1	0.8	1.0	1.3	2.5	-0.5	-0.5	-1.4	-0.5	-1.0	-0.2	0.7
	df	6.4	7.0	16.2	9.5	15.8	14.1	7.2	4.9	4.3	7.1	7.7	16.3
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	63.89	284.68	2.00	5.42	10.16	3.21	12.95	26.3605	24.47	28.95	29.11	42.00
	Mean(Present)	64.40	256.40	1.40	3.00	8.60	3.40	13.60	29.6600	25.00	29.40	29.20	39.60
IL_6_V3	t	1.7	1.2	1.8	0.5	-0.4	1.7	-0.1	0.5	-0.9	-2.1	-0.7	-1.1
	df	6.8	10.3	20.1	11.8	7.3	6.1	7.1	13.8	5.7	10.3	11.1	14.8
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	65.94	288.00	2.11	5.17	9.72	3.50	13.06	27.2450	24.39	28.83	29.06	40.39
	Mean(Present)	58.17	251.17	1.17	4.17	10.17	2.50	13.17	26.4567	25.17	29.67	29.33	44.83
IL_6_V4	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Present)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
IL_6_V5	t	2.2	1.3	1.6	0.3	-0.6	0.4	-0.1	0.8	-1.4	-2.1	0.4	-0.8
	df	6.1	6.1	21.8	7.4	5.3	4.3	4.7	11.1	4.5	12.8	9.5	10.7
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	65.84	289.16	2.05	5.05	9.68	3.32	13.05	27.2768	24.32	28.89	29.16	40.84
	Mean(Present)	57.00	239.40	1.20	4.40	10.40	3.00	13.20	26.1780	25.60	29.60	29.00	44.00
IL1_alpha_V1	T	-0.4	-0.4	0.9	-4.1	-0.5	-1.2	-1.0	0.9	1.3	0.0	-1.3	-2.2
	df	1.1	1.1	1.0	21.0	3.0	21.0	1.7	1.2	1.0	1.1	1.4	1.3
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	22	22	22	22	22	22	22	22	22
	# Missing	60.00	248.50	5.50	1.00	9.50	3.00	12.00	29.2350	27.00	29.00	28.50	29.50
	Mean(Present)	64.36	281.55	1.55	5.27	9.86	3.27	13.18	26.8491	24.36	29.05	29.18	42.59
IL1_alpha_V2	t	-1.2	-0.1	2.3	0.4	1.7	-0.2	-0.8	-0.4	1.0	-0.5	0.2	-0.6
	df	12.1	2.9	20.0	2.8	4.0	4.4	2.5	3.2	3.1	2.4	2.6	15.6
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.62	278.38	2.00	5.05	10.00	3.24	12.90	26.9419	24.67	29.00	29.14	41.29
	Mean(Present)	66.67	281.67	1.00	4.00	8.67	3.33	14.33	27.7900	24.00	29.33	29.00	43.00

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 36. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
IL_6_V1	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	1	1	1	1	1
	# Present	23	23	23	12	23	23	23	23	23	23	23	22
	# Missing	3.00	4.00	27.00	31.00	39.00	138.00	41.00	17.00	20.00	6.00	2.00	1.00
	Mean(Present)	6.74	7.39	32.43	27.67	45.83	115.52	44.39	21.13	10.78	7.04	6.04	6.68
IL_6_V2	t	0.9	0.6	-0.3	-2.8	1.0	1.9	-0.7	-0.4	0.4	1.5	0.5	0.0
	df	10.8	9.6	7.4	4.0	10.0	20.3	16.0	8.0	4.6	7.4	11.5	6.0
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.84	7.42	32.00	26.36	46.68	123.89	43.63	20.74	11.47	7.26	5.95	6.44
	Mean(Present)	5.60	6.60	33.00	36.50	41.20	88.20	46.60	21.80	10.00	6.00	5.60	6.40
IL_6_V3	t	-0.3	-0.6	-0.7		2.5	3.2	-2.0	-1.9	-0.3	0.0	-0.9	0.1
	df	15.3	13.9	9.2		10.5	21.9	8.0	12.9	6.2	7.0	7.6	9.1
	P(2-tail)	18	18	18	12	18	18	18	18	18	18	18	17
	# Present	6	6	6	1	6	6	6	6	6	6	6	6
	# Missing	6.50	7.06	31.67	27.42	49.00	131.89	41.44	19.89	10.94	7.00	5.67	6.59
	Mean(Present)	6.83	7.83	33.83	34.00	35.17	70.17	52.67	24.17	11.83	7.00	6.50	6.00
IL_6_V4	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
IL_6_V5	t	0.2	-0.1	-1.3	-2.9	3.0	3.4	-1.8	-3.0	-0.4	-0.2	-0.2	-0.1
	df	12.6	9.7	9.7	8.8	12.9	21.3	12.4	6.7	5.9	5.0	8.7	6.1
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.63	7.21	31.53	26.55	48.42	129.05	42.68	19.42	10.95	6.95	5.84	6.33
	Mean(Present)	6.40	7.40	34.80	35.50	34.60	68.60	50.20	26.80	12.00	7.20	6.00	6.80
IL1_alpha_V1	T	-5.1	-4.5	0.1	1.7	-1.3	-0.3	-0.9	-0.1	0.2	-2.0	-3.0	-2.9
	df	21.0	8.6	1.1	9.2	9.4	1.6	19.3	1.3	1.0	1.3	1.3	20.0
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	11	22	22	22	22	22	22	22	21
	# Missing	3.00	3.50	33.00	32.50	41.00	108.50	42.00	20.50	12.50	5.00	3.00	1.00
	Mean(Present)	6.91	7.59	32.14	27.09	45.95	117.18	44.45	21.00	11.05	7.18	6.14	6.95
IL1_alpha_V2	t	-0.4	-1.4	2.4		1.1	2.2	-0.7	-0.6	-0.4	0.8	-0.2	-0.5
	df	5.4	21.4	21.4		2.9	21.1	3.8	2.7	2.1	3.0	4.6	2.3
	P(2-tail)	21	21	21	13	21	21	21	21	21	21	21	20
	# Present	3	3	3	0	3	3	3	3	3	3	3	3
	# Missing	6.52	7.10	32.67	27.92	46.57	120.90	43.81	20.71	10.90	7.10	5.86	5.95
	Mean(Present)	7.00	8.33	29.00		38.33	85.33	47.33	22.67	13.00	6.33	6.00	9.67

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 37. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-sion_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
IL_6_V1	t												
	df												
	P(2-tail)	1	1	1	1	0	1	1	1	1	0	1	1
	# Present	22	23	23	20	19	0	18	17	20	19	0	18
	# Missing	14.00	5.00	1.00	3.1000	0.0000	19.0000	2.6000	7.9000	0.0700	0.0000	0.3000	0.1100
	Mean(Present)	16.73	3.91	4.00	3.4500	122.2316		3.9778	5.0706	0.0585	0.6400		0.0739
IL_6_V2	t	-0.2	1.0	0.6	-0.8	2.5				1.7	-0.3		
	df	5.6	9.1	7.6	3.1	6.7				14.3	3.4		
	P(2-tail)	18	19	19	17	15	1	19	17	17	15	1	19
	# Present	5	5	5	4	4	0	0	1	4	4	0	0
	# Missing	16.44	4.32	4.11	2.7941	141.1667	19.0000	3.9053	5.5235	0.0612	0.6100	0.3000	0.0758
	Mean(Present)	17.20	2.60	3.00	6.1500	51.2250			0.2000	0.0500	0.7525		
IL_6_V3	t	0.5	0.7	2.0	-0.4	2.0		-0.4		3.0	-0.5		1.5
	df	8.5	16.9	19.5	4.2	8.7		1.2		16.5	3.5		1.7
	P(2-tail)	17	18	18	16	15	1	17	18	16	15	1	17
	# Present	6	6	6	5	4	0	2	0	5	4	0	2
	# Missing	17.12	4.22	4.50	3.1000	136.7200	19.0000	3.7235	5.2278	0.0638	0.5913	0.3000	0.0776
	Mean(Present)	15.17	3.17	2.00	4.5000	67.9000		5.4500		0.0440	0.8225		0.0600
IL_6_V4	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
IL_6_V5	t	-0.6	0.0	0.5	-0.9	2.4		-1.0	0.9	3.1	-0.5		1.6
	df	5.6	6.1	7.0	3.1	2.3		4.6	15.3	7.8	1.0		3.5
	P(2-tail)	18	19	19	17	17	1	16	16	17	17	1	16
	# Present	5	5	5	4	2	0	3	2	4	2	0	3
	# Missing	16.06	3.95	4.05	2.7353	131.1235	19.0000	3.4938	5.4438	0.0635	0.5818	0.3000	0.0788
	Mean(Present)	18.60	4.00	3.20	6.4000	46.6500		6.1000	3.5000	0.0400	1.1350		0.0600
IL1_alpha_V1	T	-2.0	-0.6	-3.8	1.1					0.1			
	df	2.7	1.3	10.5	1.0					1.5			
	P(2-tail)	2	2	2	2	1	1	1	1	2	1	1	1
	# Present	21	22	22	19	18	0	18	17	19	18	0	18
	# Missing	12.00	2.50	0.50	10.5500	74.6000	19.0000	2.6000	7.9000	0.0600	2.1700	0.3000	0.1100
	Mean(Present)	17.05	4.09	4.18	2.6842	124.8778		3.9778	5.0706	0.0589	0.5550		0.0739
IL1_alpha_V2	t	-0.3	-0.2	1.2	2.7	1.1				2.2	1.6		
	df	2.3	3.9	4.6	18.4	1.2				3.5	2.7		
	P(2-tail)	20	21	21	19	17	1	19	18	19	17	1	19
	# Present	3	3	3	2	2	0	0	0	2	2	0	0
	# Missing	16.40	3.90	4.10	3.6789	129.3588	19.0000	3.9053	5.2278	0.0605	0.6788	0.3000	0.0758
	Mean(Present)	18.00	4.33	2.33	1.1000	61.6500				0.0450	0.3100		

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 38. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
IL_6_V1	t												
	df												
	P(2-tail)	1	1	0	1	1	1	1	0	1	1	1	1
	# Present	17	20	19	0	18	17	20	19	18	0	17	20
	# Missing	0.1400	19.5000	0.0000	16.5000	10.9000	10.8000	0.0300	0.0000	0.0300	0.0500	0.0300	14.5000
	Mean(Present)	0.0700	11.6200	18.2579		11.7833	11.2588	0.0585	0.1595	0.0550		0.0559	3.6500
IL_6_V2	t		0.1	-3.7				0.3	-1.3				-1.4
	df		14.1	12.1				5.1	3.6				3.9
	P(2-tail)	17	17	15	1	19	17	17	15	19	1	17	17
	# Present	1	4	4	0	0	1	4	4	0	0	1	4
	# Missing	0.0753	12.0294	16.3933	16.5000	11.7368	11.0529	0.0576	0.1380	0.0537	0.0500	0.0559	3.6235
	Mean(Present)	0.0500	11.8500	25.2500			14.3000	0.0550	0.2400			0.0300	6.4750
IL_6_V3	t		0.5	-4.0		-0.1		-0.8	-1.4	-1.0			-0.7
	df		18.4	7.5		1.5		11.1	3.6	1.0			5.9
	P(2-tail)	18	16	15	1	17	18	16	15	17	1	18	16
	# Present	0	5	4	0	2	0	5	4	2	0	0	5
	# Missing	0.0739	12.2000	16.0533	16.5000	11.7118	11.2333	0.0556	0.1373	0.0500	0.0500	0.0544	3.8750
	Mean(Present)		11.3400	26.5250		11.9500		0.0620	0.2425	0.0850			5.1000
IL_6_V4	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
IL_6_V5	t	1.1	2.5	0.2		0.7	0.6	-1.2	0.8	-1.9		-1.4	-0.7
	df	8.2	10.6	1.1		2.3	1.1	7.1	3.3	2.1		1.2	3.8
	P(2-tail)	16	17	17	1	16	16	17	17	16	1	16	17
	# Present	2	4	2	0	3	2	4	2	3	0	2	4
	# Missing	0.0750	12.7824	18.3941	16.5000	12.0500	11.4813	0.0553	0.1629	0.0475	0.0500	0.0513	3.8882
	Mean(Present)	0.0650	8.6500	17.1000		10.0667	9.2500	0.0650	0.1300	0.0867		0.0800	5.3500
IL1_alpha_V1	T		0.5					-1.7					6.1
	df		1.1					1.4					1.1
	P(2-tail)	1	2	1	1	1	1	2	1	1	1	1	2
	# Present	17	19	18	0	18	17	19	18	18	0	17	19
	# Missing	0.1400	14.2500	24.2000	16.5000	10.9000	10.8000	0.0400	0.1600	0.0300	0.0500	0.0300	12.9500
	Mean(Present)	0.0700	11.7579	17.9278		11.7833	11.2588	0.0589	0.1594	0.0550		0.0559	3.2421
IL1_alpha_V2	t		-0.5	-2.0				-0.6	-1.4				0.4
	df		11.4	1.5				1.2	1.0				2.0
	P(2-tail)	18	19	17	1	19	18	19	17	19	1	18	19
	# Present	0	2	2	0	0	0	2	2	0	0	0	2
	# Missing	0.0739	11.9368	17.3882	16.5000	11.7368	11.2333	0.0563	0.1394	0.0537	0.0500	0.0544	4.2263
	Mean(Present)		12.5500	25.6500				0.0650	0.3300				3.6000

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 39. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
IL_6_V1	t												
	df												
	P(2-tail)	0	1	1	1	1	1	1	1	1	1	1	1
	# Present	19	0	18	17	20	18	1	20	18	20	18	1
	# Missing	0.0000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0000	0.0000	0.0000	0.2300	0.0600	0.1800
	Mean(Present)	123.5316		3.3111	3.0118	0.0630	0.0439	0.0200	4.6210	0.0289	0.1070	0.1311	0.3200
IL_6_V2	t	-1.1				1.6	2.0		1.0	1.1	-0.3	-2.6	
	df	3.1				16.0	15.0		18.0	6.9	4.2	2.6	
	P(2-tail)	15	1	19	17	17	16	1	19	17	17	16	1
	# Present	4	0	0	1	4	3	1	2	2	4	3	1
	# Missing	86.9267	32.8000	3.4000	3.5412	0.0741	0.0494	0.0000	4.8632	0.0294	0.1100	0.1094	0.1800
	Mean(Present)	260.8000			3.4000	0.0000	0.0000	0.0200	0.0100	0.0100	0.1250	0.2233	0.3200
IL_6_V3	t	0.5		0.9		1.6	2.0		1.0		0.7	-1.2	
	df	13.8		3.7		15.0	15.0		17.0		6.5	2.8	
	P(2-tail)	15	1	17	18	16	16	1	18	18	16	16	1
	# Present	4	0	2	0	5	3	1	3	1	5	3	1
	# Missing	129.6467	32.8000	3.4882	3.5333	0.0788	0.0494	0.0000	5.1333	0.0278	0.1200	0.1188	0.1800
	Mean(Present)	100.6000		2.6500		0.0000	0.0000	0.0200	0.0067	0.0200	0.0900	0.1733	0.3200
IL_6_V4	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
IL_6_V5	t	2.9		1.4	0.2	-0.7			1.0	-0.1	-1.0		
	df	16.9		13.2	1.6	3.3			16.0	4.3	4.6		
	P(2-tail)	17	1	16	16	17	19	1	17	16	17	19	1
	# Present	2	0	3	2	4	0	1	4	3	4	0	1
	# Missing	135.7412	32.8000	3.5813	3.5688	0.0400	0.0416	0.0000	5.4329	0.0269	0.1047	0.1274	0.1800
	Mean(Present)	19.7500		2.4333	3.2500	0.1450		0.0200	0.0150	0.0300	0.1475		0.3200
IL1_alpha_V1	T					-1.6			-1.0	-1.1	7.6		
	df					18.0			18.0	6.9	18.7		
	P(2-tail)	1	1	1	1	2	1	2	2	2	2	1	2
	# Present	18	0	18	17	19	18	0	19	17	19	18	0
	# Missing	28.2000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0100	0.0100	0.0100	0.2350	0.0600	0.2500
	Mean(Present)	128.8278		3.3111	3.0118	0.0663	0.0439		4.8632	0.0294	0.1000	0.1311	
IL1_alpha_V2	t	-0.6				1.6	2.0				3.7	-1.3	
	df	5.8				18.0	16.0				18.0	1.2	
	P(2-tail)	17	1	19	18	19	17	2	21	19	19	17	2
	# Present	2	0	0	0	2	2	0	0	0	2	2	0
	# Missing	120.2412	32.8000	3.4000	3.5333	0.0663	0.0465	0.0100	4.4010	0.0274	0.1195	0.1188	0.2500
	Mean(Present)	151.5000				0.0000	0.0000				0.0500	0.2000	

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 40. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
IL_6_V1	t												
	df												
	P(2-tail)	1	1	1	1	1	1	1	0	1	1	0	0
	# Present	20	13	20	18	1	20	18	0	23	1	0	0
	# Missing	0.1100	0.0900	5.2700	3.8800	8.8200	5.7400	9.3500	0.0000	14.9100	10.2300	0.0000	0.0000
	Mean(Present)	0.0680	0.0700	2.6975	2.6411	2.5200	2.7040	2.6589		10.0309	8.8600		
IL_6_V2	t	0.9		-0.8	-0.6		0.0	-0.3		1.0			
	df	1.8		3.5	2.1		1.2	9.5		8.0			
	P(2-tail)	19	13	17	16	1	19	17	0	19	1	0	0
	# Present	2	1	4	3	1	2	2	0	5	1	0	0
	# Missing	0.0737	0.0746	2.6776	2.5988	8.8200	2.8489	2.9918	0.0000	10.5253	10.2300	0.0000	0.0000
	Mean(Present)	0.0350	0.0300	3.4250	3.2800	2.5200	2.8450	3.1750		9.1280	8.8600		
IL_6_V3	t	-0.4		0.4	1.7		-1.3			1.0			
	df	12.9		14.2	15.4		3.4			11.3			
	P(2-tail)	18	14	16	16	1	18	18	0	18	1	0	0
	# Present	3	0	5	3	1	3	1	0	6	1	0	0
	# Missing	0.0683	0.0714	2.8619	2.7875	8.8200	2.7517	2.9867	0.0000	10.5839	10.2300	0.0000	0.0000
	Mean(Present)	0.0800		2.6860	2.2733	2.5200	3.4300	3.4500		9.1850	8.8600		
IL_6_V4	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
IL_6_V5	t	-0.8		0.5			-0.5	0.7		-0.1			
	df	4.2		5.9			4.7	8.7		5.0			
	P(2-tail)	17	13	17	19	1	17	16	0	19	1	0	0
	# Present	4	1	4	0	1	4	3	0	5	1	0	0
	# Missing	0.0624	0.0715	2.8729	2.7063	8.8200	2.7959	3.0769	0.0000	10.1684	10.2300	0.0000	0.0000
	Mean(Present)	0.1025	0.0700	2.5950		2.5200	3.0725	2.6600		10.4840	8.8600		
IL1_alpha_V1	T	0.8		1.4			2.0	1.3		0.0			
	df	4.2		1.1			1.1	1.0		1.0			
	P(2-tail)	2	1	2	1	2	2	2	0	2	2	0	0
	# Present	19	13	19	18	0	19	17	0	22	0	0	0
	# Missing	0.0900	0.0900	4.2250	3.8800	5.6700	4.7250	6.4000	0.0000	10.3650	9.5450	0.0000	0.0000
	Mean(Present)	0.0679	0.0700	2.6721	2.6411		2.6511	2.6124		10.2223			
IL1_alpha_V2	t			1.9	2.2					0.9			
	df			9.1	10.5					4.3			
	P(2-tail)	21	14	19	17	2	21	19	0	21	2	0	0
	# Present	0	0	2	2	0	0	0	0	3	0	0	0
	# Missing	0.0700	0.0714	2.8800	2.7706	5.6700	2.8486	3.0111	0.0000	10.3914	9.5450	0.0000	0.0000
	Mean(Present)			2.2500	2.1600					9.1333			

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 41. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5
IL1_alpha_V3	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Present)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
IL1_alpha_V4	t	2.2	1.3	1.6	0.3	-0.6	0.4	-0.1	0.8	-1.4	-2.1	0.4	-0.8
	df	6.1	6.1	21.8	7.4	5.3	4.3	4.7	11.1	4.5	12.8	9.5	10.7
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	65.84	289.16	2.05	5.05	9.68	3.32	13.05	27.2768	24.32	28.89	29.16	40.84
	Mean(Present)	57.00	239.40	1.20	4.40	10.40	3.00	13.20	26.1780	25.60	29.60	29.00	44.00
IL1_alpha_V5	t	-0.4	-0.4	0.9	-4.1	-0.5	-1.2	-1.0	0.9	1.3	0.0	-1.3	-2.2
	df	1.1	1.1	1.0	21.0	3.0	21.0	1.7	1.2	1.0	1.1	1.4	1.3
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	22	22	22	22	22	22	22	22	22
	# Missing	60.00	248.50	5.50	1.00	9.50	3.00	12.00	29.2350	27.00	29.00	28.50	29.50
	Mean(Present)	64.36	281.55	1.55	5.27	9.86	3.27	13.18	26.8491	24.36	29.05	29.18	42.59
IL1_beta_V1	t	-1.2	-0.1	2.3	0.4	1.7	-0.2	-0.8	-0.4	1.0	-0.5	0.2	-0.6
	df	12.1	2.9	20.0	2.8	4.0	4.4	2.5	3.2	3.1	2.4	2.6	15.6
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.62	278.38	2.00	5.05	10.00	3.24	12.90	26.9419	24.67	29.00	29.14	41.29
	Mean(Present)	66.67	281.67	1.00	4.00	8.67	3.33	14.33	27.7900	24.00	29.33	29.00	43.00
IL1_beta_V2	t	4.0	0.1	1.8	-0.5	-1.2	1.3	-0.5	0.5	-0.6	-1.5	-0.3	-1.4
	df	12.7	18.0	14.1	13.9	16.7	13.5	16.6	20.4	11.3	17.2	22.0	22.0
	P(2-tail)	14	14	14	14	14	14	14	14	14	14	14	14
	# Present	10	10	10	10	10	10	10	10	10	10	10	10
	# Missing	68.86	280.57	2.36	4.50	9.43	3.50	12.86	27.3779	24.43	28.79	29.07	39.07
	Mean(Present)	57.20	276.30	1.20	5.50	10.40	2.90	13.40	26.5860	24.80	29.40	29.20	44.90
IL1_beta_V3	T	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Present)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
IL1_beta_V4	t	2.2	1.3	1.6	0.3	-0.6	0.4	-0.1	0.8	-1.4	-2.1	0.4	-0.8
	df	6.1	6.1	21.8	7.4	5.3	4.3	4.7	11.1	4.5	12.8	9.5	10.7
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	65.84	289.16	2.05	5.05	9.68	3.32	13.05	27.2768	24.32	28.89	29.16	40.84
	Mean(Present)	57.00	239.40	1.20	4.40	10.40	3.00	13.20	26.1780	25.60	29.60	29.00	44.00

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 42. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
IL1_alpha_V3	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
IL1_alpha_V4	t	0.2	-0.1	-1.3	-2.9	3.0	3.4	-1.8	-3.0	-0.4	-0.2	-0.2	-0.1
	df	12.6	9.7	9.7	8.8	12.9	21.3	12.4	6.7	5.9	5.0	8.7	6.1
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.63	7.21	31.53	26.55	48.42	129.05	42.68	19.42	10.95	6.95	5.84	6.33
	Mean(Present)	6.40	7.40	34.80	35.50	34.60	68.60	50.20	26.80	12.00	7.20	6.00	6.80
IL1_alpha_V5	t	-5.1	-4.5	0.1	1.7	-1.3	-0.3	-0.9	-0.1	0.2	-2.0	-3.0	-2.9
	df	21.0	8.6	1.1	9.2	9.4	1.6	19.3	1.3	1.0	1.3	1.3	20.0
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	11	22	22	22	22	22	22	22	21
	# Missing	3.00	3.50	33.00	32.50	41.00	108.50	42.00	20.50	12.50	5.00	3.00	1.00
	Mean(Present)	6.91	7.59	32.14	27.09	45.95	117.18	44.45	21.00	11.05	7.18	6.14	6.95
IL1_beta_V1	t	-0.4	-1.4	2.4		1.1	2.2	-0.7	-0.6	-0.4	0.8	-0.2	-0.5
	df	5.4	21.4	21.4		2.9	21.1	3.8	2.7	2.1	3.0	4.6	2.3
	P(2-tail)	21	21	21	13	21	21	21	21	21	21	21	20
	# Present	3	3	3	0	3	3	3	3	3	3	3	3
	# Missing	6.52	7.10	32.67	27.92	46.57	120.90	43.81	20.71	10.90	7.10	5.86	5.95
	Mean(Present)	7.00	8.33	29.00		38.33	85.33	47.33	22.67	13.00	6.33	6.00	9.67
IL1_beta_V2	t	-1.2	-1.1	-1.6		1.5	1.2	-1.1	-2.3	-0.3	0.4	-1.0	-0.7
	df	21.1	21.8	22.0		17.9	20.6	14.8	20.7	17.7	18.2	21.5	16.3
	P(2-tail)	14	14	14	12	14	14	14	14	14	14	14	13
	# Present	10	10	10	1	10	10	10	10	10	10	10	10
	# Missing	5.93	6.64	30.57	27.42	49.14	130.07	41.93	18.86	10.86	7.14	5.57	5.15
	Mean(Present)	7.50	8.10	34.50	34.00	40.50	97.40	47.50	23.90	11.60	6.80	6.30	8.10
IL1_beta_V3	T	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
IL1_beta_V4	t	0.2	-0.1	-1.3	-2.9	3.0	3.4	-1.8	-3.0	-0.4	-0.2	-0.2	-0.1
	df	12.6	9.7	9.7	8.8	12.9	21.3	12.4	6.7	5.9	5.0	8.7	6.1
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.63	7.21	31.53	26.55	48.42	129.05	42.68	19.42	10.95	6.95	5.84	6.33
	Mean(Present)	6.40	7.40	34.80	35.50	34.60	68.60	50.20	26.80	12.00	7.20	6.00	6.80

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 43. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-sion_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
IL1_alpha_V3	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
IL1_alpha_V4	t	-0.6	0.0	0.5	-0.9	2.4		-1.0	0.9	3.1	-0.5		1.6
	df	5.6	6.1	7.0	3.1	2.3		4.6	15.3	7.8	1.0		3.5
	P(2-tail)	18	19	19	17	17	1	16	16	17	17	1	16
	# Present	5	5	5	4	2	0	3	2	4	2	0	3
	# Missing	16.06	3.95	4.05	2.7353	131.1235	19.0000	3.4938	5.4438	0.0635	0.5818	0.3000	0.0788
	Mean(Present)	18.60	4.00	3.20	6.4000	46.6500		6.1000	3.5000	0.0400	1.1350		0.0600
IL1_alpha_V5	t	-2.0	-0.6	-3.8	1.1					0.1			
	df	2.7	1.3	10.5	1.0					1.5			
	P(2-tail)	2	2	2	2	1	1	1	1	2	1	1	1
	# Present	21	22	22	19	18	0	18	17	19	18	0	18
	# Missing	12.00	2.50	0.50	10.5500	74.6000	19.0000	2.6000	7.9000	0.0600	2.1700	0.3000	0.1100
	Mean(Present)	17.05	4.09	4.18	2.6842	124.8778		3.9778	5.0706	0.0589	0.5550		0.0739
IL1_beta_V1	t	-0.3	-0.2	1.2	2.7	1.1				2.2	1.6		
	df	2.3	3.9	4.6	18.4	1.2				3.5	2.7		
	P(2-tail)	20	21	21	19	17	1	19	18	19	17	1	19
	# Present	3	3	3	2	2	0	0	0	2	2	0	0
	# Missing	16.40	3.90	4.10	3.6789	129.3588	19.0000	3.9053	5.2278	0.0605	0.6788	0.3000	0.0758
	Mean(Present)	18.00	4.33	2.33	1.1000	61.6500				0.0450	0.3100		
IL1_beta_V2	t	0.6	-0.5	-0.1	0.4	1.5		0.4	1.6	0.8	-0.5		1.0
	df	17.6	21.9	18.8	9.9	16.9		16.9	15.4	13.6	10.4		10.8
	P(2-tail)	14	14	14	12	12	1	13	14	12	12	1	13
	# Present	9	10	10	9	7	0	6	4	9	7	0	6
	# Missing	17.36	3.64	3.79	3.7750	141.3250	19.0000	4.2308	6.1214	0.0625	0.5850	0.3000	0.0792
	Mean(Present)	15.44	4.40	4.00	2.9778	89.5000		3.2000	2.1000	0.0544	0.7343		0.0683
IL1_beta_V3	T	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
IL1_beta_V4	t	-0.6	0.0	0.5	-0.9	2.4		-1.0	0.9	3.1	-0.5		1.6
	df	5.6	6.1	7.0	3.1	2.3		4.6	15.3	7.8	1.0		3.5
	P(2-tail)	18	19	19	17	17	1	16	16	17	17	1	16
	# Present	5	5	5	4	2	0	3	2	4	2	0	3
	# Missing	16.06	3.95	4.05	2.7353	131.1235	19.0000	3.4938	5.4438	0.0635	0.5818	0.3000	0.0788
	Mean(Present)	18.60	4.00	3.20	6.4000	46.6500		6.1000	3.5000	0.0400	1.1350		0.0600

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 44. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
IL1_alpha_V3	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
IL1_alpha_V4	t	1.1	2.5	0.2		0.7	0.6	-1.2	0.8	-1.9		-1.4	-0.7
	df	8.2	10.6	1.1		2.3	1.1	7.1	3.3	2.1		1.2	3.8
	P(2-tail)	16	17	17	1	16	16	17	17	16	1	16	17
	# Present	2	4	2	0	3	2	4	2	3	0	2	4
	# Missing	0.0750	12.7824	18.3941	16.5000	12.0500	11.4813	0.0553	0.1629	0.0475	0.0500	0.0513	3.8882
	Mean(Present)	0.0650	8.6500	17.1000		10.0667	9.2500	0.0650	0.1300	0.0867		0.0800	5.3500
IL1_alpha_V5	t		0.5					-1.7					6.1
	df		1.1					1.4					1.1
	P(2-tail)	1	2	1	1	1	1	2	1	1	1	1	2
	# Present	17	19	18	0	18	17	19	18	18	0	17	19
	# Missing	0.1400	14.2500	24.2000	16.5000	10.9000	10.8000	0.0400	0.1600	0.0300	0.0500	0.0300	12.9500
	Mean(Present)	0.0700	11.7579	17.9278		11.7833	11.2588	0.0589	0.1594	0.0550		0.0559	3.2421
IL1_beta_V1	t		-0.5	-2.0				-0.6	-1.4				0.4
	df		11.4	1.5				1.2	1.0				2.0
	P(2-tail)	18	19	17	1	19	18	19	17	19	1	18	19
	# Present	0	2	2	0	0	0	2	2	0	0	0	2
	# Missing	0.0739	11.9368	17.3882	16.5000	11.7368	11.2333	0.0563	0.1394	0.0537	0.0500	0.0544	4.2263
	Mean(Present)		12.5500	25.6500				0.0650	0.3300				3.6000
IL1_beta_V2	t	0.3	0.8	-2.2		-1.0	-0.7	-0.4	-0.6	-1.3		0.5	0.5
	df	5.1	13.1	12.9		9.3	5.2	18.6	9.7	7.0		7.8	18.4
	P(2-tail)	14	12	12	1	13	14	12	12	13	1	14	12
	# Present	4	9	7	0	6	4	9	7	6	0	4	9
	# Missing	0.0750	12.6250	15.7500	16.5000	11.2692	10.9786	0.0558	0.1467	0.0485	0.0500	0.0557	4.5000
	Mean(Present)	0.0700	11.1556	22.5571		12.7500	12.1250	0.0589	0.1814	0.0650		0.0500	3.7222
IL1_beta_V3	T	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
IL1_beta_V4	t	1.1	2.5	0.2		0.7	0.6	-1.2	0.8	-1.9		-1.4	-0.7
	df	8.2	10.6	1.1		2.3	1.1	7.1	3.3	2.1		1.2	3.8
	P(2-tail)	16	17	17	1	16	16	17	17	16	1	16	17
	# Present	2	4	2	0	3	2	4	2	3	0	2	4
	# Missing	0.0750	12.7824	18.3941	16.5000	12.0500	11.4813	0.0553	0.1629	0.0475	0.0500	0.0513	3.8882
	Mean(Present)	0.0650	8.6500	17.1000		10.0667	9.2500	0.0650	0.1300	0.0867		0.0800	5.3500

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 45. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
IL1_alpha_V3	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
IL1_alpha_V4	t	2.9		1.4	0.2	-0.7			1.0	-0.1	-1.0		
	df	16.9		13.2	1.6	3.3			16.0	4.3	4.6		
	P(2-tail)	17	1	16	16	17	19	1	17	16	17	19	1
	# Present	2	0	3	2	4	0	1	4	3	4	0	1
	# Missing	135.7412	32.8000	3.5813	3.5688	0.0400	0.0416	0.0000	5.4329	0.0269	0.1047	0.1274	0.1800
	Mean(Present)	19.7500		2.4333	3.2500	0.1450		0.0200	0.0150	0.0300	0.1475		0.3200
IL1_alpha_V5	t					-1.6			-1.0	-1.1	7.6		
	df					18.0			18.0	6.9	18.7		
	P(2-tail)	1	1	1	1	2	1	2	2	2	2	1	2
	# Present	18	0	18	17	19	18	0	19	17	19	18	0
	# Missing	28.2000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0100	0.0100	0.0100	0.2350	0.0600	0.2500
	Mean(Present)	128.8278		3.3111	3.0118	0.0663	0.0439		4.8632	0.0294	0.1000	0.1311	
IL1_beta_V1	t	-0.6				1.6	2.0				3.7	-1.3	
	df	5.8				18.0	16.0				18.0	1.2	
	P(2-tail)	17	1	19	18	19	17	2	21	19	19	17	2
	# Present	2	0	0	0	2	2	0	0	0	2	2	0
	# Missing	120.2412	32.8000	3.4000	3.5333	0.0663	0.0465	0.0100	4.4010	0.0274	0.1195	0.1188	0.2500
	Mean(Present)	151.5000				0.0000	0.0000				0.0500	0.2000	
IL1_beta_V2	t	1.0		0.8	1.0	1.7	1.7		-1.0	-2.1	-0.2	0.5	
	df	13.4		16.7	11.6	11.0	13.1		6.0	4.9	13.2	8.3	
	P(2-tail)	12	1	13	14	12	13	1	14	14	12	13	1
	# Present	7	0	6	4	9	6	1	7	5	9	6	1
	# Missing	144.4333	32.8000	3.6385	3.7500	0.1050	0.0577	0.0000	0.0407	0.0100	0.1100	0.1338	0.1800
	Mean(Present)	87.7000		2.8833	2.7750	0.0000	0.0067	0.0200	13.1214	0.0760	0.1167	0.1133	0.3200
IL1_beta_V3	T	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
IL1_beta_V4	t	2.9		1.4	0.2	-0.7			1.0	-0.1	-1.0		
	df	16.9		13.2	1.6	3.3			16.0	4.3	4.6		
	P(2-tail)	17	1	16	16	17	19	1	17	16	17	19	1
	# Present	2	0	3	2	4	0	1	4	3	4	0	1
	# Missing	135.7412	32.8000	3.5813	3.5688	0.0400	0.0416	0.0000	5.4329	0.0269	0.1047	0.1274	0.1800
	Mean(Present)	19.7500		2.4333	3.2500	0.1450		0.0200	0.0150	0.0300	0.1475		0.3200

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 46. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
IL1_alpha_V3	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
IL1_alpha_V4	t	-0.8		0.5			-0.5	0.7		-0.1			
	df	4.2		5.9			4.7	8.7		5.0			
	P(2-tail)	17	13	17	19	1	17	16	0	19	1	0	0
	# Present	4	1	4	0	1	4	3	0	5	1	0	0
	# Missing	0.0624	0.0715	2.8729	2.7063	8.8200	2.7959	3.0769	0.0000	10.1684	10.2300	0.0000	0.0000
	Mean(Present)	0.1025	0.0700	2.5950		2.5200	3.0725	2.6600		10.4840	8.8600		
IL1_alpha_V5	t	0.8		1.4			2.0	1.3		0.0			
	df	4.2		1.1			1.1	1.0		1.0			
	P(2-tail)	2	1	2	1	2	2	2	0	2	2	0	0
	# Present	19	13	19	18	0	19	17	0	22	0	0	0
	# Missing	0.0900	0.0900	4.2250	3.8800	5.6700	4.7250	6.4000	0.0000	10.3650	9.5450	0.0000	0.0000
	Mean(Present)	0.0679	0.0700	2.6721	2.6411		2.6511	2.6124		10.2223			
IL1_beta_V1	t			1.9	2.2					0.9			
	df			9.1	10.5					4.3			
	P(2-tail)	21	14	19	17	2	21	19	0	21	2	0	0
	# Present	0	0	2	2	0	0	0	0	3	0	0	0
	# Missing	0.0700	0.0714	2.8800	2.7706	5.6700	2.8486	3.0111	0.0000	10.3914	9.5450	0.0000	0.0000
	Mean(Present)			2.2500	2.1600					9.1333			
IL1_beta_V2	t	0.7		1.7	2.2		0.0	1.6		0.6			
	df	17.8		15.7	16.8		18.0	17.0		18.9			
	P(2-tail)	14	14	12	13	1	14	14	0	14	1	0	0
	# Present	7	0	9	6	1	7	5	0	10	1	0	0
	# Missing	0.0771	0.0714	3.1492	2.9408	8.8200	2.8529	3.2600	0.0000	10.5936	10.2300	0.0000	0.0000
	Mean(Present)	0.0557		2.3811	2.1983	2.5200	2.8400	2.3140		9.7310	8.8600		
IL1_beta_V3	T	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
IL1_beta_V4	t	-0.8		0.5			-0.5	0.7		-0.1			
	df	4.2		5.9			4.7	8.7		5.0			
	P(2-tail)	17	13	17	19	1	17	16	0	19	1	0	0
	# Present	4	1	4	0	1	4	3	0	5	1	0	0
	# Missing	0.0624	0.0715	2.8729	2.7063	8.8200	2.7959	3.0769	0.0000	10.1684	10.2300	0.0000	0.0000
	Mean(Present)	0.1025	0.0700	2.5950		2.5200	3.0725	2.6600		10.4840	8.8600		

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 47. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5
IL1_beta_V6	t	4.0	0.1	1.8	-0.5	-1.2	1.3	-0.5	0.5	-0.6	-1.5	-0.3	-1.4
	df	12.7	18.0	14.1	13.9	16.7	13.5	16.6	20.4	11.3	17.2	22.0	22.0
	P(2-tail)	14	14	14	14	14	14	14	14	14	14	14	14
	# Present	10	10	10	10	10	10	10	10	10	10	10	10
	# Missing	68.86	280.57	2.36	4.50	9.43	3.50	12.86	27.3779	24.43	28.79	29.07	39.07
	Mean(Present)	57.20	276.30	1.20	5.50	10.40	2.90	13.40	26.5860	24.80	29.40	29.20	44.90
TNF_alpha_V1	t	-2.3	0.9	1.1	0.5	0.1	-1.4	-1.4	0.2	-0.2	-0.5	0.2	-0.5
	df	15.5	2.4	11.5	2.7	2.2	2.6	2.4	3.6	6.1	2.4	2.6	20.7
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.33	284.43	1.95	5.10	9.86	3.14	12.76	27.0838	24.57	29.00	29.14	41.33
	Mean(Present)	68.67	239.33	1.33	3.67	9.67	4.00	15.33	26.7967	24.67	29.33	29.00	42.67
TNF_alpha_V2	t	2.2	1.3	1.6	0.3	-0.6	0.4	-0.1	0.8	-1.4	-2.1	0.4	-0.8
	df	6.1	6.1	21.8	7.4	5.3	4.3	4.7	11.1	4.5	12.8	9.5	10.7
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	65.84	289.16	2.05	5.05	9.68	3.32	13.05	27.2768	24.32	28.89	29.16	40.84
	Mean(Present)	57.00	239.40	1.20	4.40	10.40	3.00	13.20	26.1780	25.60	29.60	29.00	44.00
TNF_alpha_V3	t	-0.4	-0.4	0.9	-4.1	-0.5	-1.2	-1.0	0.9	1.3	0.0	-1.3	-2.2
	df	1.1	1.1	1.0	21.0	3.0	21.0	1.7	1.2	1.0	1.1	1.4	1.3
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	22	22	22	22	22	22	22	22	22
	# Missing	60.00	248.50	5.50	1.00	9.50	3.00	12.00	29.2350	27.00	29.00	28.50	29.50
	Mean(Present)	64.36	281.55	1.55	5.27	9.86	3.27	13.18	26.8491	24.36	29.05	29.18	42.59
TNF_alpha_V4	t	-1.2	-0.1	2.3	0.4	1.7	-0.2	-0.8	-0.4	1.0	-0.5	0.2	-0.6
	df	12.1	2.9	20.0	2.8	4.0	4.4	2.5	3.2	3.1	2.4	2.6	15.6
	P(2-tail)	21	21	21	21	21	21	21	21	21	21	21	21
	# Present	3	3	3	3	3	3	3	3	3	3	3	3
	# Missing	63.62	278.38	2.00	5.05	10.00	3.24	12.90	26.9419	24.67	29.00	29.14	41.29
	Mean(Present)	66.67	281.67	1.00	4.00	8.67	3.33	14.33	27.7900	24.00	29.33	29.00	43.00
TNF_alpha_V5	T	1.1	0.5	1.6	0.1	-0.6	1.5	-0.1	0.5	0.5	-1.5	-0.7	-1.9
	df	5.3	9.3	21.8	8.1	5.2	4.6	5.0	8.5	9.8	6.9	7.1	13.6
	P(2-tail)	19	19	19	19	19	19	19	19	19	19	19	19
	# Present	5	5	5	5	5	5	5	5	5	5	5	5
	# Missing	65.11	281.63	2.05	4.95	9.68	3.47	13.05	27.2232	24.63	28.89	29.05	40.11
	Mean(Present)	59.80	268.00	1.20	4.80	10.40	2.40	13.20	26.3820	24.40	29.60	29.40	46.80
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	24	24	24	24	24	24	24	24	24
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0000	0.00	0.00	0.00	0.00
	Mean(Present)	64.00	278.79	1.88	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 48. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
IL1_beta_V6	t	-1.2	-1.1	-1.6		1.5	1.2	-1.1	-2.3	-0.3	0.4	-1.0	-0.7
	df	21.1	21.8	22.0		17.9	20.6	14.8	20.7	17.7	18.2	21.5	16.3
	P(2-tail)	14	14	14	12	14	14	14	14	14	14	14	13
	# Present	10	10	10	1	10	10	10	10	10	10	10	10
	# Missing	5.93	6.64	30.57	27.42	49.14	130.07	41.93	18.86	10.86	7.14	5.57	5.15
	Mean(Present)	7.50	8.10	34.50	34.00	40.50	97.40	47.50	23.90	11.60	6.80	6.30	8.10
TNF_alpha_V1	t	1.0	-0.1	0.0	0.7	-0.5	-0.2	0.6	-0.1	1.6	1.1	1.1	-0.6
	df	4.2	3.0	3.0	4.6	2.9	2.5	7.5	2.5	5.7	2.7	11.0	1.1
	P(2-tail)	21	21	21	11	21	21	21	21	21	21	21	21
	# Present	3	3	3	2	3	3	3	3	3	3	3	2
	# Missing	6.76	7.24	32.19	28.36	45.10	115.52	44.52	20.90	11.52	7.14	5.95	5.81
	Mean(Present)	5.33	7.33	32.33	25.50	48.67	123.00	42.33	21.33	8.67	6.00	5.33	13.00
TNF_alpha_V2	t	0.2	-0.1	-1.3	-2.9	3.0	3.4	-1.8	-3.0	-0.4	-0.2	-0.2	-0.1
	df	12.6	9.7	9.7	8.8	12.9	21.3	12.4	6.7	5.9	5.0	8.7	6.1
	P(2-tail)	19	19	19	11	19	19	19	19	19	19	19	18
	# Present	5	5	5	2	5	5	5	5	5	5	5	5
	# Missing	6.63	7.21	31.53	26.55	48.42	129.05	42.68	19.42	10.95	6.95	5.84	6.33
	Mean(Present)	6.40	7.40	34.80	35.50	34.60	68.60	50.20	26.80	12.00	7.20	6.00	6.80
TNF_alpha_V3	t	-5.1	-4.5	0.1	1.7	-1.3	-0.3	-0.9	-0.1	0.2	-2.0	-3.0	-2.9
	df	21.0	8.6	1.1	9.2	9.4	1.6	19.3	1.3	1.0	1.3	1.3	20.0
	P(2-tail)	2	2	2	2	2	2	2	2	2	2	2	2
	# Present	22	22	22	11	22	22	22	22	22	22	22	21
	# Missing	3.00	3.50	33.00	32.50	41.00	108.50	42.00	20.50	12.50	5.00	3.00	1.00
	Mean(Present)	6.91	7.59	32.14	27.09	45.95	117.18	44.45	21.00	11.05	7.18	6.14	6.95
TNF_alpha_V4	t	-0.4	-1.4	2.4		1.1	2.2	-0.7	-0.6	-0.4	0.8	-0.2	-0.5
	df	5.4	21.4	21.4		2.9	21.1	3.8	2.7	2.1	3.0	4.6	2.3
	P(2-tail)	21	21	21	13	21	21	21	21	21	21	21	20
	# Present	3	3	3	0	3	3	3	3	3	3	3	3
	# Missing	6.52	7.10	32.67	27.92	46.57	120.90	43.81	20.71	10.90	7.10	5.86	5.95
	Mean(Present)	7.00	8.33	29.00		38.33	85.33	47.33	22.67	13.00	6.33	6.00	9.67
TNF_alpha_V5	T	-1.1	-2.0	-0.2		2.5	3.1	-2.2	-1.6	-0.8	-0.7	-1.5	-0.1
	df	18.1	21.8	6.6		7.0	20.5	5.7	8.0	4.8	5.8	6.0	6.1
	P(2-tail)	19	19	19	13	19	19	19	19	19	19	19	18
	# Present	5	5	5	0	5	5	5	5	5	5	5	5
	# Missing	6.32	6.84	32.05	27.92	48.68	129.11	41.53	20.11	10.63	6.84	5.58	6.28
	Mean(Present)	7.60	8.80	32.80		33.60	68.40	54.60	24.20	13.20	7.60	7.00	7.00
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	13	24	24	24	24	24	24	24	23
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Mean(Present)	6.58	7.25	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 49. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-sion_Scale	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
IL1_beta_V6	t	7	-0.5	-0.1	0.4	1.5		0.4	1.6	0.8	-0.5		1.0
	df	17.6	21.9	18.8	9.9	16.9		16.9	15.4	13.6	10.4		10.8
	P(2-tail)	14	14	14	12	12	1	13	14	12	12	1	13
	# Present	9	10	10	9	7	0	6	4	9	7	0	6
	# Missing	17.36	3.64	3.79	3.7750	141.3250	19.0000	4.2308	6.1214	0.0625	0.5850	0.3000	0.0792
	Mean(Present)	15.44	4.40	4.00	2.9778	89.5000		3.2000	2.1000	0.0544	0.7343		0.0683
TNF_al-pha_V1	t	-1.7	-0.8	-0.6		-6.6		1.4	0.6		-0.2		1.6
	df	2.3	2.6	2.8		16.3		16.3	3.2		5.7		4.9
	P(2-tail)	20	21	21	21	17	1	17	16	21	17	1	17
	# Present	3	3	3	0	2	0	2	2	0	2	0	2
	# Missing	15.40	3.71	3.71	3.4333	108.8471	19.0000	4.1588	5.4313	0.0590	0.6353	0.3000	0.0771
	Mean(Present)	24.67	5.67	5.00		236.0000		1.7500	3.6000		0.6800		0.0650
TNF_al-pha_V2	t	-0.6	0.0	0.5	-0.9	2.4		-1.0	0.9	3.1	-0.5		1.6
	df	5.6	6.1	7.0	3.1	2.3		4.6	15.3	7.8	1.0		3.5
	P(2-tail)	18	19	19	17	17	1	16	16	17	17	1	16
	# Present	5	5	5	4	2	0	3	2	4	2	0	3
	# Missing	16.06	3.95	4.05	2.7353	131.1235	19.0000	3.4938	5.4438	0.0635	0.5818	0.3000	0.0788
	Mean(Present)	18.60	4.00	3.20	6.4000	46.6500		6.1000	3.5000	0.0400	1.1350		0.0600
TNF_al-pha_V3	t	-2.0	-0.6	-3.8	1.1					0.1			
	df	2.7	1.3	10.5	1.0					1.5			
	P(2-tail)	2	2	2	2	1	1	1	1	2	1	1	1
	# Present	21	22	22	19	18	0	18	17	19	18	0	18
	# Missing	12.00	2.50	0.50	10.5500	74.6000	19.0000	2.6000	7.9000	0.0600	2.1700	0.3000	0.1100
	Mean(Present)	17.05	4.09	4.18	2.6842	124.8778		3.9778	5.0706	0.0589	0.5550		0.0739
TNF_al-pha_V4	t	-0.3	-0.2	1.2	2.7	1.1				2.2	1.6		
	df	2.3	3.9	4.6	18.4	1.2				3.5	2.7		
	P(2-tail)	20	21	21	19	17	1	19	18	19	17	1	19
	# Present	3	3	3	2	2	0	0	0	2	2	0	0
	# Missing	16.40	3.90	4.10	3.6789	129.3588	19.0000	3.9053	5.2278	0.0605	0.6788	0.3000	0.0758
	Mean(Present)	18.00	4.33	2.33	1.1000	61.6500				0.0450	0.3100		
TNF_al-pha_V5	T	0.1	0.1	1.5	2.7	1.6		-0.4		3.0	1.6		1.5
	df	6.0	15.2	16.2	16.6	3.7		1.2		10.7	10.3		1.7
	P(2-tail)	18	19	19	17	16	1	17	18	17	16	1	17
	# Present	5	5	5	4	3	0	2	0	4	3	0	2
	# Missing	16.72	4.00	4.26	3.9765	132.8375	19.0000	3.7235	5.2278	0.0629	0.6900	0.3000	0.0776
	Mean(Present)	16.20	3.80	2.40	1.1250	65.6667		5.4500		0.0425	0.3733		0.0600
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	23	24	24	21	19	1	19	18	21	19	1	19
	# Missing	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	16.61	3.96	3.88	3.4333	122.2316	19.0000	3.9053	5.2278	0.0590	0.6400	0.3000	0.0758

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 50. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
IL1_beta_V6	t	0.3	0.8	-2.2		-1.0	-0.7	-0.4	-0.6	-1.3		0.5	0.5
	df	5.1	13.1	12.9		9.3	5.2	18.6	9.7	7.0		7.8	18.4
	P(2-tail)	14	12	12	1	13	14	12	12	13	1	14	12
	# Present	4	9	7	0	6	4	9	7	6	0	4	9
	# Missing	0.0750	12.6250	15.7500	16.5000	11.2692	10.9786	0.0558	0.1467	0.0485	0.0500	0.0557	4.5000
	Mean(Present)	0.0700	11.1556	22.5571		12.7500	12.1250	0.0589	0.1814	0.0650		0.0500	3.7222
TNF_alpha_V1	t	0.3		5.2		0.4	0.6		1.0	0.6		-0.3	
	df	2.5		16.7		16.8	9.5		1.4	1.3		1.1	
	P(2-tail)	16	21	17	1	17	16	21	17	17	1	16	21
	# Present	2	0	2	0	2	2	0	2	2	0	2	0
	# Missing	0.0744	11.9952	19.2471	16.5000	11.7706	11.2938	0.0571	0.1665	0.0547	0.0500	0.0531	4.1667
	Mean(Present)	0.0700		9.8500		11.4500	10.7500		0.1000	0.0450		0.0650	
TNF_alpha_V2	t	1.1	2.5	0.2		0.7	0.6	-1.2	0.8	-1.9		-1.4	-0.7
	df	8.2	10.6	1.1		2.3	1.1	7.1	3.3	2.1		1.2	3.8
	P(2-tail)	16	17	17	1	16	16	17	17	16	1	16	17
	# Present	2	4	2	0	3	2	4	2	3	0	2	4
	# Missing	0.0750	12.7824	18.3941	16.5000	12.0500	11.4813	0.0553	0.1629	0.0475	0.0500	0.0513	3.8882
	Mean(Present)	0.0650	8.6500	17.1000		10.0667	9.2500	0.0650	0.1300	0.0867		0.0800	5.3500
TNF_alpha_V3	t		0.5					-1.7					6.1
	df		1.1					1.4					1.1
	P(2-tail)	1	2	1	1	1	1	2	1	1	1	1	2
	# Present	17	19	18	0	18	17	19	18	18	0	17	19
	# Missing	0.1400	14.2500	24.2000	16.5000	10.9000	10.8000	0.0400	0.1600	0.0300	0.0500	0.0300	12.9500
	Mean(Present)	0.0700	11.7579	17.9278		11.7833	11.2588	0.0589	0.1594	0.0550		0.0559	3.2421
TNF_alpha_V4	t		-0.5	-2.0				-0.6	-1.4				0.4
	df		11.4	1.5				1.2	1.0				2.0
	P(2-tail)	18	19	17	1	19	18	19	17	19	1	18	19
	# Present	0	2	2	0	0	0	2	2	0	0	0	2
	# Missing	0.0739	11.9368	17.3882	16.5000	11.7368	11.2333	0.0563	0.1394	0.0537	0.0500	0.0544	4.2263
	Mean(Present)		12.5500	25.6500				0.0650	0.3300				3.6000
TNF_alpha_V5	T		0.1	-3.4		-0.1		-1.2	-1.3	-1.0			0.7
	df		16.9	3.7		1.5		7.1	2.2	1.0			12.0
	P(2-tail)	18	17	16	1	17	18	17	16	17	1	18	17
	# Present	0	4	3	0	2	0	4	3	2	0	0	4
	# Missing	0.0739	12.0118	16.5625	16.5000	11.7118	11.2333	0.0553	0.1388	0.0500	0.0500	0.0544	4.3176
	Mean(Present)		11.9250	27.3000		11.9500		0.0650	0.2700	0.0850			3.5250
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	18	21	19	1	19	18	21	19	19	1	18	21
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0739	11.9952	18.2579	16.5000	11.7368	11.2333	0.0571	0.1595	0.0537	0.0500	0.0544	4.1667

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 51. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
IL1_beta_V6	t	1.0		0.8	1.0	1.7	1.7		-1.0	-2.1	-0.2	0.5	
	df	13.4		16.7	11.6	11.0	13.1		6.0	4.9	13.2	8.3	
	P(2-tail)	12	1	13	14	12	13	1	14	14	12	13	1
	# Present	7	0	6	4	9	6	1	7	5	9	6	1
	# Missing	144.4333	32.8000	3.6385	3.7500	0.1050	0.0577	0.0000	0.0407	0.0100	0.1100	0.1338	0.1800
	Mean(Present)	87.7000		2.8833	2.7750	0.0000	0.0067	0.0200	13.1214	0.0760	0.1167	0.1133	0.3200
TNF_alpha_V1	t	1.4		1.5	2.6		-0.6		1.0	2.2		1.9	
	df	16.0		9.0	15.0		1.1		18.0	16.0		3.3	
	P(2-tail)	17	1	17	16	21	17	2	19	17	21	17	2
	# Present	2	0	2	2	0	2	0	2	2	0	2	0
	# Missing	129.2471	32.8000	3.5176	3.7250	0.0600	0.0347	0.0100	4.8642	0.0306	0.1129	0.1329	0.2500
	Mean(Present)	74.9500		2.4000	2.0000		0.1000		0.0000	0.0000		0.0800	
TNF_alpha_V2	t	2.9		1.4	0.2	-0.7			1.0	-0.1	-1.0		
	df	16.9		13.2	1.6	3.3			16.0	4.3	4.6		
	P(2-tail)	17	1	16	16	17	19	1	17	16	17	19	1
	# Present	2	0	3	2	4	0	1	4	3	4	0	1
	# Missing	135.7412	32.8000	3.5813	3.5688	0.0400	0.0416	0.0000	5.4329	0.0269	0.1047	0.1274	0.1800
	Mean(Present)	19.7500		2.4333	3.2500	0.1450		0.0200	0.0150	0.0300	0.1475		0.3200
TNF_alpha_V3	t					-1.6			-1.0	-1.1	7.6		
	df					18.0			18.0	6.9	18.7		
	P(2-tail)	1	1	1	1	2	1	2	2	2	2	1	2
	# Present	18	0	18	17	19	18	0	19	17	19	18	0
	# Missing	28.2000	32.8000	5.0000	12.4000	0.0000	0.0000	0.0100	0.0100	0.0100	0.2350	0.0600	0.2500
	Mean(Present)	128.8278		3.3111	3.0118	0.0663	0.0439		4.8632	0.0294	0.1000	0.1311	
TNF_alpha_V4	t	-0.6				1.6	2.0				3.7	-1.3	
	df	5.8				18.0	16.0				18.0	1.2	
	P(2-tail)	17	1	19	18	19	17	2	21	19	19	17	2
	# Present	2	0	0	0	2	2	0	0	0	2	2	0
	# Missing	120.2412	32.8000	3.4000	3.5333	0.0663	0.0465	0.0100	4.4010	0.0274	0.1195	0.1188	0.2500
	Mean(Present)	151.5000				0.0000	0.0000				0.0500	0.2000	
TNF_alpha_V5	T	0.0		0.9		1.6	2.0		1.0		3.6	-1.2	
	df	10.5		3.7		16.0	15.0		18.0		16.5	2.8	
	P(2-tail)	16	1	17	18	17	16	2	19	19	17	16	2
	# Present	3	0	2	0	4	3	0	2	0	4	3	0
	# Missing	123.3063	32.8000	3.4882	3.5333	0.0741	0.0494	0.0100	4.8642	0.0274	0.1271	0.1188	0.2500
	Mean(Present)	124.7333		2.6500		0.0000	0.0000		0.0000		0.0525	0.1733	
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	19	1	19	18	21	19	2	21	19	21	19	2
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	123.5316	32.8000	3.4000	3.5333	0.0600	0.0416	0.0100	4.4010	0.0274	0.1129	0.1274	0.2500

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 52. Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
IL1_beta_V6	t	0.7		1.7	2.2		0.0	1.6		0.6			
	df	17.8		15.7	16.8		18.0	17.0		18.9			
	P(2-tail)	14	14	12	13	1	14	14	0	14	1	0	0
	# Present	7	0	9	6	1	7	5	0	10	1	0	0
	# Missing	0.0771	0.0714	3.1492	2.9408	8.8200	2.8529	3.2600	0.0000	10.5936	10.2300	0.0000	0.0000
	Mean(Present)	0.0557		2.3811	2.1983	2.5200	2.8400	2.3140		9.7310	8.8600		
TNF_alpha_V1	t	1.9	1.6		1.4		2.4	1.8		3.6			
	df	4.1	2.5		1.3		2.1	3.0		21.5			
	P(2-tail)	19	12	21	17	2	19	17	0	21	2	0	0
	# Present	2	2	0	2	0	2	2	0	3	0	0	0
	# Missing	0.0753	0.0758	2.8200	2.8053	5.6700	2.9474	3.1382	0.0000	10.5995	9.5450	0.0000	0.0000
	Mean(Present)	0.0200	0.0450		1.8650		1.9100	1.9300		7.6767			
TNF_alpha_V2	t	-0.8		0.5			-0.5	0.7		-0.1			
	df	4.2		5.9			4.7	8.7		5.0			
	P(2-tail)	17	13	17	19	1	17	16	0	19	1	0	0
	# Present	4	1	4	0	1	4	3	0	5	1	0	0
	# Missing	0.0624	0.0715	2.8729	2.7063	8.8200	2.7959	3.0769	0.0000	10.1684	10.2300	0.0000	0.0000
	Mean(Present)	0.1025	0.0700	2.5950		2.5200	3.0725	2.6600		10.4840	8.8600		
TNF_alpha_V3	t	0.8		1.4			2.0	1.3		0.0			
	df	4.2		1.1			1.1	1.0		1.0			
	P(2-tail)	2	1	2	1	2	2	2	0	2	2	0	0
	# Present	19	13	19	18	0	19	17	0	22	0	0	0
	# Missing	0.0900	0.0900	4.2250	3.8800	5.6700	4.7250	6.4000	0.0000	10.3650	9.5450	0.0000	0.0000
	Mean(Present)	0.0679	0.0700	2.6721	2.6411		2.6511	2.6124		10.2223			
TNF_alpha_V4	t			1.9	2.2					0.9			
	df			9.1	10.5					4.3			
	P(2-tail)	21	14	19	17	2	21	19	0	21	2	0	0
	# Present	0	0	2	2	0	0	0	0	3	0	0	0
	# Missing	0.0700	0.0714	2.8800	2.7706	5.6700	2.8486	3.0111	0.0000	10.3914	9.5450	0.0000	0.0000
	Mean(Present)			2.2500	2.1600					9.1333			
TNF_alpha_V5	T	-0.5		0.7	1.7		-0.6			0.4			
	df	2.9		8.6	15.4		1.2			9.4			
	P(2-tail)	19	14	17	16	2	19	19	0	19	2	0	0
	# Present	2	0	4	3	0	2	0	0	5	0	0	0
	# Missing	0.0684	0.0714	2.8806	2.7875	5.6700	2.8021	3.0111	0.0000	10.3332	9.5450	0.0000	0.0000
	Mean(Present)	0.0850		2.5625	2.2733		3.2900			9.8580			
LZ_V1	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	21	14	21	19	2	21	19	0	24	2	0	0
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0700	0.0714	2.8200	2.7063	5.6700	2.8486	3.0111		10.2342	9.5450		

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 53. Separate Variance t Tests[a]

		Age	Length_Surgery	LOS_ICU	LOS_Hosp	Secondary_Edu_Yrs	Tertiary_Edu_Yrs	Edu_Yrs_Total	BMI	mmstot_V1	mmstot_V4	mmstot_V5	VLMT_Learning_V5
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	24	24	24	24	24	24	24	24	24
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0000	0.00	0.00	0.00	0.00
	Mean(Present)	64.00	278.79	1.88	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	24	24	24	24	24	24	24	24	24
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0000	0.00	0.00	0.00	0.00
	Mean(Present)	64.00	278.79	1.88	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	24	24	24	24	24	24	24	24	24
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0000	0.00	0.00	0.00	0.00
	Mean(Present)	64.00	278.79	1.88	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	24	24	24	24	24	24	24	24	24
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.0000	0.00	0.00	0.00	0.00
	Mean(Present)	64.00	278.79	1.88	4.92	9.83	3.25	13.08	27.0479	24.58	29.04	29.13	41.50
infectyn	t	-0.9	1.3	-0.9	2.1	2.6	1.2	1.9	0.8	-1.2	1.5	-0.1	1.7
	df	8.0	7.7	5.2	19.5	21.0	17.0	22.0	12.5	5.7	7.9	12.5	7.2
	P(2-tail)	18	18	18	18	18	18	18	18	18	18	18	18
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	63.00	290.89	1.56	5.72	10.22	3.33	13.44	27.3589	24.33	29.22	29.11	43.72
	Mean(Present)	67.00	242.50	2.83	2.50	8.67	3.00	12.00	26.1150	25.33	28.50	29.17	34.83

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 54. Separate Variance t Tests[a]

		vlmtdg6r_V5	vlmtdg7r_V5	wms4vw1tot_V5	wms4vw2tot_V6	TMT_A_V5	TMT_B_V5	sdmctot_V5	vfatot_V5	cervfg_V5	wmsdsf_V5	wmsdsb_V5	BAI_Tot_V5
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	13	24	24	24	24	24	24	24	23
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Mean(Present)	6.58	7.25	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	13	24	24	24	24	24	24	24	23
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Mean(Present)	6.58	7.25	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	13	24	24	24	24	24	24	24	23
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Mean(Present)	6.58	7.25	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	24	24	24	13	24	24	24	24	24	24	24	23
	# Missing	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Mean(Present)	6.58	7.25	32.21	27.92	45.54	116.46	44.25	20.96	11.17	7.00	5.88	6.43
infectyn	t	1.6	1.6	1.1	0.4	0.7	-1.2	0.6	-0.2	-0.3	0.7	2.5	1.9
	df	7.6	8.0	6.2	9.4	11.0	6.7	8.9	8.4	6.7	7.5	6.7	19.5
	P(2-tail)	18	18	18	7	18	18	18	18	18	18	18	17
	# Present	6	6	6	6	6	6	6	6	6	6	6	6
	# Missing	7.28	7.94	33.28	28.86	46.61	104.61	45.11	20.83	10.94	7.17	6.44	7.76
	Mean(Present)	4.50	5.17	29.00	26.83	42.33	152.00	41.67	21.33	11.83	6.50	4.17	2.67

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 55. Separate Variance t Tests[a]

		PTSS_10_Tot	PHQ_D_ Somatic_Scale	PHQ_D_ Depres-	CRP_V1	CRP_V2	CRP_V3	CRP_V4	CRP_V5	PCT_V1	PCT_V2	PCT_V3	PCT_V4
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	23	24	24	21	19	1	19	18	21	19	1	19
	# Missing	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	16.61	3.96	3.88	3.4333	122.2316	19.0000	3.9053	5.2278	0.0590	0.6400	0.3000	0.0758
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	23	24	24	21	19	1	19	18	21	19	1	19
	# Missing	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	16.61	3.96	3.88	3.4333	122.2316	19.0000	3.9053	5.2278	0.0590	0.6400	0.3000	0.0758
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	23	24	24	21	19	1	19	18	21	19	1	19
	# Missing	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	16.61	3.96	3.88	3.4333	122.2316	19.0000	3.9053	5.2278	0.0590	0.6400	0.3000	0.0758
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	23	24	24	21	19	1	19	18	21	19	1	19
	# Missing	0.00	0.00	0.00	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	16.61	3.96	3.88	3.4333	122.2316	19.0000	3.9053	5.2278	0.0590	0.6400	0.3000	0.0758
infectyn	t	2.2	2.6	3.1	-1.8	-0.2		1.0	0.5	-1.2	-1.9		-0.7
	df	20.9	20.0	21.9	4.3	7.3		17.0	16.0	7.8	4.2		7.7
	P(2-tail)	17	18	18	16	14	0	14	13	16	14	0	14
	# Present	6	6	6	5	5	1	5	5	5	5	1	5
	# Missing	17.88	4.78	4.72	2.2313	120.4357	0.0000	4.4857	5.6231	0.0563	0.4393	0.0000	0.0736
	Mean(Present)	13.00	1.50	1.33	7.2800	127.2600	19.0000	2.2800	4.2000	0.0680	1.2020	0.3000	0.0820

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 56. Separate Variance t Tests[a]

		PCT_V5	NSE_V1	NSE_V2	NSE_V3	NSE_V4	NSE_V5	S100_V1	S100_V2	S100_V4	S100_V3	S100_V5	IL_6_V1
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	18	21	19	1	19	18	21	19	19	1	18	21
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0739	11.9952	18.2579	16.5000	11.7368	11.2333	0.0571	0.1595	0.0537	0.0500	0.0544	4.1667
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	18	21	19	1	19	18	21	19	19	1	18	21
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0739	11.9952	18.2579	16.5000	11.7368	11.2333	0.0571	0.1595	0.0537	0.0500	0.0544	4.1667
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	18	21	19	1	19	18	21	19	19	1	18	21
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0739	11.9952	18.2579	16.5000	11.7368	11.2333	0.0571	0.1595	0.0537	0.0500	0.0544	4.1667
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	18	21	19	1	19	18	21	19	19	1	18	21
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	0.0739	11.9952	18.2579	16.5000	11.7368	11.2333	0.0571	0.1595	0.0537	0.0500	0.0544	4.1667
infectyn	t	-1.0	-0.9	0.9		1.3	1.6	1.2	0.7	0.4		-0.8	-1.9
	df	6.2	4.1	8.6		6.8	7.9	6.6	15.3	6.4		5.5	4.2
	P(2-tail)	13	16	14	0	14	13	16	14	14	0	13	16
	# Present	5	5	5	1	5	5	5	5	5	1	5	5
	# Missing	0.0692	11.0563	19.1214	0.0000	12.2857	11.8385	0.0600	0.1664	0.0550	0.0000	0.0508	3.1000
	Mean(Present)	0.0860	15.0000	15.8400	16.5000	10.2000	9.6600	0.0480	0.1400	0.0500	0.0500	0.0640	7.5800

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 57. Separate Variance t Tests[a]

		IL_6_V2	IL_6_V3	IL_6_V4	IL_6_V5	IL1_alpha_V1	IL1_alpha_V2	IL1_alpha_V3	IL1_alpha_V4	IL1_alpha_V5	IL1_beta_V1	IL1_beta_V2	IL1_beta_V3
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	19	1	19	18	21	19	2	21	19	21	19	2
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	123.5316	32.8000	3.4000	3.5333	0.0600	0.0416	0.0100	4.4010	0.0274	0.1129	0.1274	0.2500
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	19	1	19	18	21	19	2	21	19	21	19	2
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	123.5316	32.8000	3.4000	3.5333	0.0600	0.0416	0.0100	4.4010	0.0274	0.1129	0.1274	0.2500
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	19	1	19	18	21	19	2	21	19	21	19	2
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	123.5316	32.8000	3.4000	3.5333	0.0600	0.0416	0.0100	4.4010	0.0274	0.1129	0.1274	0.2500
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	19	1	19	18	21	19	2	21	19	21	19	2
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	Mean(Present)	123.5316	32.8000	3.4000	3.5333	0.0600	0.0416	0.0100	4.4010	0.0274	0.1129	0.1274	0.2500
infectyn	t	1.4		0.7	-0.7	-0.6	-0.6		1.0	2.0	-2.1	0.0	
	df	16.8		15.1	4.3	4.8	3.3		14.0	12.9	6.6	6.6	
	P(2-tail)	14	0	14	13	16	15	0	15	13	16	15	0
	# Present	5	1	5	5	5	4	2	6	6	5	4	2
	# Missing	143.0429	0.0000	3.5714	3.1308	0.0425	0.0307	0.0000	6.1600	0.0385	0.0931	0.1273	0.0000
	Mean(Present)	68.9000	32.8000	2.9200	4.5800	0.1160	0.0825	0.0100	0.0033	0.0033	0.1760	0.1275	0.2500

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 58.s Separate Variance t Tests[a]

		IL1_beta_V4	IL1_beta_V6	TNF_alpha_V1	TNF_alpha_V2	TNF_alpha_V3	TNF_alpha_V4	TNF_alpha_V5	LZ_V1	LZ_V2	LZ_V3	LZ_V4	LZ_V5
LZ_V4	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	21	14	21	19	2	21	19	0	24	2	0	0
	# Missing	0,0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.00000	.00000	.0000
	Mean(Pre-sent)	0.0700	0.0714	2.8200	2.7063	5.6700	2.8486	3.0111		10.2342	9.5450		
LZ_V5	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	21	14	21	19	2	21	19	0	24	2	0	0
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.00000	.00000	.0000
	Mean(Pre-sent)	0.0700	0.0714	2.8200	2.7063	5.6700	2.8486	3.0111		10.2342	9.5450		
pumpyn	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	21	14	21	19	2	21	19	0	24	2	0	0
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.00000	.00000	.0000
	Mean(Pre-sent)	0.0700	0.0714	2.8200	2.7063	5.6700	2.8486	3.0111		10.2342	9.5450		
Stroke	t												
	df												
	P(2-tail)	0	0	0	0	0	0	0	0	0	0	0	0
	# Present	21	14	21	19	2	21	19	0	24	2	0	0
	# Missing	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.00000	.00000	.0000
	Mean(Pre-sent)	0.0700	0.0714	2.8200	2.7063	5.6700	2.8486	3.0111		10.2342	9.5450		
infectyn	t	-1.8	-0.9	-1.4	-1.9		-1.3	-1.5		0.2			
	df	5.6	12.0	5.7	8.3		6.6	5.6		8.7			
	P(2-tail)	15	9	16	15	0	15	13	0	18	0	0	0
	# Present	6	5	5	4	2	6	6	0	6	2	0	0
	# Missing	0.0427	0.0656	2.5988	2.5453	0.0000	2.6280	2.4746	0.0000	10.3217	0.00000	.00000	.0000
	Mean(Pre-sent)	0.1383	0.0820	3.5280	3.3100	5.6700	3.4000	4.1733		9.9717	9.5450		

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 59. Percent Mismatch of Indicator Variables.[a.b]

	CRP_V1	PCT_V1	NSE_V1	S100_V1	IL_6_V1	IL1_alpha_V1	IL1_beta_V1	TNF_alpha_V1	IL1_alpha_V4	IL1_beta_V4	TNF_alpha_V4	NSE_V4	S100_V4	CRP_V4	IL_6_V4	PCT_V4	S100_V5	IL_6_V5	CRP_V5	NSE_V5	PCT_V5
CRP_V1	12.50																				
PCT_V1	0.00	12.50																			
NSE_V1	0.00	0.00	12.50																		
S100_V1	0.00	0.00	0.00	12.50																	
IL_6_V1	0.00	0.00	0.00	0.00	12.50																
IL1_alpha_V1	0.00	0.00	0.00	0.00	0.00	12.50															
IL1_beta_V1	0.00	0.00	0.00	0.00	0.00	0.00	12.50														
TNF_alpha_V1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	12.50													
IL1_alpha_V4	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67	12.50												
IL1_beta_V4	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67	0.00	12.50											
TNF_alpha_V4	16.67	16.67	16.67	16.67	16.67	16.67	16.67	16.67	0.00	0.00	12.50										
NSE_V4	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	20.83									
S100_V4	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	0.00	20.83								
CRP_V4	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	0.00	0.00	20.83							
IL_6_V4	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	0.00	0.00	0.00	20.83						
PCT_V4	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	0.00	0.00	0.00	0.00	20.83					
S100_V5	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50	25.00				
IL_6_V5	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50	0.00	25.00			
CRP_V5	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50	0.00	0.00	25.00		
NSE_V5	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50	0.00	0.00	0.00	25.00	
PCT_V5	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	12.50	12.50	12.50	12.50	12.50	12.50	12.50	12.50	0.00	0.00	0.00	0.00	25.00
IL1_alpha_V5	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	16.67	16.67	16.67	16.67	16.67	4.17	4.17	4.17	4.17	4.17

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables. *a. Variables are sorted on missing patterns. b. Indicator variables with less than 5% missing values are not displayed.*

Table 60. Percent Mismatch of Indicator Variables.[a.b]

	CRP_V1	PCT_V1	NSE_V1	S100_V1	IL_6_V1	IL1_al-pha_V1	IL1_beta_V1	TNF_al-pha_V1	IL1_al-pha_V4	IL1_beta_V4	TNF_al-pha_V4	NSE_V4	S100_V4	CRP_V4	IL_6_V4	PCT_V4	S100_V5	IL_6_V5	CRP_V5	NSE_V5	PCT_V5
TNF_alpha_V5	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	8.33	8.33	8.33	16.67	16.67	16.67	16.67	16.67	4.17	4.17	4.17	4.17	4.17
IL1_beta_V6	45.83	45.83	45.83	45.83	45.83	45.83	45.83	45.83	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	16.67	16.67	16.67	16.67	16.67
wms4vw2tot_V6	50.00	50.00	50.00	50.00	50.00	50.00	50.00	50.00	33.33	33.33	33.33	41.67	41.67	41.67	41.67	41.67	29.17	29.17	29.17	29.17	29.17
S100_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	33.33	33.33	33.33	33.33	33.33	29.17	29.17	29.17	29.17	29.17
NSE_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	33.33	33.33	33.33	33.33	33.33	29.17	29.17	29.17	29.17	29.17
CRP_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	33.33	33.33	33.33	33.33	33.33	29.17	29.17	29.17	29.17	29.17
PCT_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	33.33	33.33	33.33	33.33	33.33	29.17	29.17	29.17	29.17	29.17
IL_6_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	33.33	33.33	33.33	33.33	33.33	29.17	29.17	29.17	29.17	29.17
IL1_alpha_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	20.83	20.83	20.83	20.83	20.83
IL1_beta_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	20.83	20.83	20.83	20.83	20.83
TNF_alpha_V2	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	25.00	20.83	20.83	20.83	20.83	20.83
infectyn	29.17	29.17	29.17	29.17	29.17	29.17	29.17	29.17	37.50	37.50	37.50	37.50	37.50	37.50	37.50	37.50	41.67	41.67	41.67	41.67	41.67
LZ_V1	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
LZ_V4	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
LZ_V5	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
pumpyn	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
Stroke	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	87.50	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
CRP_V3	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	75.00	75.00	70.83	70.83	70.83	70.83	70.83
PCT_V3	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	75.00	75.00	70.83	70.83	70.83	70.83	70.83
S100_V3	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	75.00	75.00	70.83	70.83	70.83	70.83	70.83
IL_6_V3	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	75.00	75.00	70.83	70.83	70.83	70.83	70.83
NSE_V3	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	75.00	75.00	70.83	70.83	70.83	70.83	70.83

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables. a. Variables are sorted on missing patterns. b. Indicator variables with less than 5% missing values are not displayed.

Table 61. Percent Mismatch of Indicator Variables.[a.b]

	CRP_V1	PCT_V1	NSE_V1	S100_V1	IL_6_V1	IL1_alpha_V1	IL1_beta_V1	TNF_alpha_V1	IL1_alpha_V4	IL1_beta_V4	TNF_alpha_V4	NSE_V4	S100_V4	CRP_V4	IL_6_V4	PCT_V4	S100_V5	IL_6_V5	CRP_V5	NSE_V5	PCT_V5
IL1_alpha_V3	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
LZ_V3	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
TNF_alpha_V3	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00
IL1_beta_V3	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	75.00	75.00	75.00	75.00

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 62. Percent Mismatch of Indicator Variables.[a.b]

	IL1_alpha_V5	TNF_alpha_V5	IL1_beta_V6	wms4vw2tot_V6	S100_V2	NSE_V2	CRP_V2	PCT_V2	IL_6_V2	IL1_alpha_V2	IL1_beta_V2	TNF_alpha_V2	infectyn	LZ_V1	LZ_V4	LZ_V5	pumpyn	Stroke	CRP_V3	PCT_V3	S100_V3
IL1_alpha_V5	20.83																				
TNF_alpha_V5	0.00	20.83																			
IL1_beta_V6	20.83	20.83	41.67																		
wms4vw2tot_V6	25.00	25.00	12.50	45.83																	
S100_V2	25.00	25.00	37.50	33.33	20.83																
NSE_V2	25.00	25.00	37.50	33.33	0.00	20.83															
CRP_V2	25.00	25.00	37.50	33.33	0.00	0.00	20.83														
PCT_V2	25.00	25.00	37.50	33.33	0.00	0.00	0.00	20.83													
IL_6_V2	25.00	25.00	37.50	33.33	0.00	0.00	0.00	0.00	20.83												
IL1_alpha_V2	25.00	25.00	29.17	41.67	16.67	16.67	16.67	16.67	16.67	20.83											
IL1_beta_V2	25.00	25.00	29.17	41.67	16.67	16.67	16.67	16.67	16.67	0.00	20.83										
TNF_alpha_V2	25.00	25.00	29.17	41.67	16.67	16.67	16.67	16.67	16.67	0.00	0.00	20.83									
infectyn	45.83	45.83	58.33	70.83	37.50	37.50	37.50	37.50	37.50	29.17	29.17	29.17	25.00								
LZ_V1	79.17	79.17	58.33	54.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	100.00							
LZ_V4	79.17	79.17	58.33	54.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	0.00	100.00						
LZ_V5	79.17	79.17	58.33	54.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	0.00	0.00	100.00					
pumpyn	79.17	79.17	58.33	54.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	0.00	0.00	0.00	100.00				
Stroke	79.17	79.17	58.33	54.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	75.00	0.00	0.00	0.00	0.00	100.00			
CRP_V3	75.00	75.00	54.17	50.00	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	79.17	4.17	4.17	4.17	4.17	4.17	95.83		
PCT_V3	75.00	75.00	54.17	50.00	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	79.17	4.17	4.17	4.17	4.17	4.17	0.00	95.83	
S100_V3	75.00	75.00	54.17	50.00	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	79.17	4.17	4.17	4.17	4.17	4.17	0.00	0.00	95.83

IL_6_V3	75.00	75.00	54.17	50.00	83.33	83.33	83.33	83.33	83.33	75.00	75.00	75.00	79.17	4.17	4.17	4.17	4.17	4.17	0.00	0.00	0.00

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 63. Percent Mismatch of Indicator Variables.[a.b]

	IL1_alpha_V5	TNF_alpha_V5	IL1_beta_V6	wms4vw2tot_V6	S100_V2	NSE_V2	CRP_V2	PCT_V2	IL_6_V2	IL1_alpha_V2	IL1_beta_V2	TNF_alpha_V2	infectyn	LZ_V1	LZ_V4	LZ_V5	pumpyn	Stroke	CRP_V3	PCT_V3	S100_V3
IL1_alpha_V3	70.83	70.83	58.33	45.83	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	83.33	8.33	8.33	8.33	8.33	8.33	4.17	4.17	4.17
LZ_V3	70.83	70.83	58.33	45.83	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	83.33	8.33	8.33	8.33	8.33	8.33	4.17	4.17	4.17
TNF_alpha_V3	70.83	70.83	58.33	45.83	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	83.33	8.33	8.33	8.33	8.33	8.33	4.17	4.17	4.17
IL1_beta_V3	70.83	70.83	58.33	45.83	79.17	79.17	79.17	79.17	79.17	79.17	79.17	79.17	83.33	8.33	8.33	8.33	8.33	8.33	4.17	4.17	4.17

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables. a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 64. Percent Mismatch of Indicator Variables.a.b

	IL_6_V3	NSE_V3	IL1_alpha_V3	LZ_V3	TNF_alpha_V3	IL1_beta_V3
S100_V3	95.83					
IL_6_V3	0.00	95.83				
NSE_V3	4.17	4.17	91.67			
IL1_alpha_V3	4.17	4.17	0.00	91.67		
LZ_V3	4.17	4.17	0.00	0.00	91.67	
TNF_alpha_V3	4.17	4.17	0.00	0.00	0.00	91.67

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 65. Separate Variance t Tests for all participantss[a]

		MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
Tel. MMSE post-OP	t	1.6	.	-.3	-1.3	.4
	df	44.1	.	173.9	46.9	56.7
	# Present	188	188	188	183	188
	# Missing	36	0	35	36	36
	Mean(Present)	27.22	18.99	7.8636	7.5889	239.81
	Mean(Missing)	26.19	.	8.0471	11.8222	235.92
Blood Sample	t	-3.6	-2.5	-.7	.3	-.8
	df	28.7	28.1	18.9	20.4	19.8
	# Present	206	171	205	201	206
	# Missing	18	17	18	18	18
	Mean(Present)	26.93	18.89	7.7807	8.3786	238.10
	Mean(Missing)	28.50	20.06	9.1644	7.2367	251.61

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Indicator variables with less than 5% missing are not displayed.

Table 66. Crosstabulations of Categorical Versus Indicator SIRS or Sepsis for all participants

			Total	0	1	Missing	
						SysMis	999
Tel. MMSE post-OP	Present	Count	188	155	29	0	4
		Percent	83.2	86.1	74.4	.0	80.0
	Missing	% SysMis	8.4	6.1	15.4	100.0	.0
		% 999	8.4	7.8	10.3	.0	20.0
Blood Sample	Present	Count	208	165	37	2	4
		Percent	92.0	91.7	94.9	100.0	80.0
	Missing	% SysMis	3.1	2.8	2.6	.0	20.0
		% Missing	4.9	5.6	2.6	.0	.0

Indicator variables with less than 5% missing are not displayed.

Table 67. Blood Sample for all participants

			Total	Pre-OP	Post-OP	Missing	
						SysMis	Missing
Tel. MMSE post-OP	Present	Count	188	140	31	6	11
		Percent	83.2	81.4	86.1	85.7	100.0
	Missing	% SysMis	8.4	10.5	2.8	.0	.0
		% 999	8.4	8.1	11.1	14.3	.0

Indicator variables with less than 5% missing are not displayed.

Table 68. Percent Mismatch of Indicator Variables for all participants.[a.b]

	Blood Sample	Tel. MMSE post-OP
Blood Sample	7.96	
Tel. MMSE post-OP	23.89	16.81

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Variables are sorted on missing patterns.

b. Indicator variables with less than 5% missing values are not displayed.

Table 69. Missing Value Codes in Pattern Tables

	Pattern Codes
	A
SIRS or Sepsis	999
MMSE pre-OP Total	999
Tel. MMSE post-OP	999
Leukocytes	999.00
CRP	999.00

System missing values are marked with S.

In the data pattern table that follows which displays individual cases. the following symbols are used:

+. Extremely high value
-. Extremely low value
S. System-missing value
A. First type of user-missing value
B. Second type of user-missing value
C. Third type of user-missing value

Table 70. Data Patterns for all participants (all cases)

			Missing and Extreme Value Patterns							
Case	Missing	Missing	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Chronic Thrombosis	SIRS or Sepsis	Blood Sample
68	1	14.3							S
69	1	14.3							S
78	1	14.3							S
79	1	14.3							S
116	1	14.3							S
1	0	.0							
6	0	.0							
7	0	.0							
8	0	.0							
10	0	.0							
12	0	.0							
14	0	.0							
16	0	.0							
17	0	.0							
18	0	.0							
19	0	.0							
22	0	.0				+			
23	0	.0							
26	0	.0				+			
27	0	.0							
31	0	.0							
32	0	.0							
33	0	.0							
34	0	.0							
35	0	.0					+		
37	0	.0				+			
38	1	14.3		S					
39	0	.0							
40	1	14.3		A					
42	0	.0							
43	0	.0							
44	0	.0							
45	0	.0				+			
46	1	14.3		A					
49	1	14.3		S					
50	0	.0							
53	0	.0							
55	1	14.3				A			
57	0	.0							
59	0	.0							
71	0	.0							
73	0	.0							
75	1	14.3		A					
77	0	.0							
78	0	.0							
79	0	.0							
80	0	.0							
81	0	.0							
83	0	.0							
84	0	.0							
85	0	.0							
86	0	.0							
89	0	.0							
91	0	.0							
93	0	.0							
96	1	14.3		S	+				
98	0	.0							
99	0	.0							
105	0	.0				+			
106	1	14.3		A					
109	0	.0							
110	1	14.3				A	+		
111	0	.0							
112	0	.0							
113	0	.0							

114	0	.0					+	
115	0	.0						
116	0	.0						
117	0	.0						
118	1	14.3	-		S			
120	0	.0						
121	1	14.3			S			
122	0	.0						
124	0	.0						
125	0	.0						
126	0	.0						
131	0	.0						
135	1	14.3			A			
139	0	.0						
140	1	14.3			A			
142	0	.0						
143	0	.0						
145	0	.0						
147	0	.0						
148	1	14.3					S	
149	0	.0						
150	0	.0						
152	0	.0						
153	0	.0						
154	0	.0						
155	0	.0						
157	0	.0						
158	1	14.3			A			
162	0	.0						
164	0	.0						
165	0	.0						
169	0	.0					+	+
170	1	14.3			A			
176	1	14.3			A			
178	0	.0						
179	0	.0						
182	0	.0						
184	0	.0						
186	0	.0						
188	0	.0						
189	0	.0						
191	0	.0						
192	0	.0						
193	0	.0						
194	0	.0						
195	0	.0					+	
196	0	.0						
201	0	.0						
203	0	.0						
204	1	14.3			S		+	
205	0	.0						
206	1	14.3			S			
208	1	14.3			S			
209	1	14.3			S			
210	0	.0				+		
212	0	.0						
214	0	.0						
215	0	.0					+	
216	0	.0						
217	0	.0						
218	0	.0						
220	2	28.6			A	A		
221	0	.0						
223	0	.0						
225	0	.0						
227	0	.0						
228	0	.0						
229	1	14.3			S			
230	0	.0						
233	0	.0						
234	0	.0						
235	0	.0						
236	1	14.3			S			
239	0	.0						
241	0	.0						

15	0	.0										
29	0	.0										
41	0	.0										
51	0	.0		-								
58	0	.0										
62	0	.0										
66	0	.0										
70	0	.0										
123	0	.0										
137	0	.0										
159	0	.0										
160	0	.0										
166	0	.0										
167	1	14.3		A								
171	0	.0										
172	1	14.3		A								
173	0	.0										
174	0	.0										
175	1	14.3	-	A								
180	0	.0					+					
181	1	14.3	-				S		+			
185	0	.0										
190	0	.0										
197	0	.0										
199	0	.0										
200	1	14.3		A								
213	0	.0										
222	0	.0										
231	0	.0										
242	0	.0										
48	1	14.3										A
138	1	14.3										A
183	1	14.3										A
198	1	14.3					+					A
211	1	14.3										A
226	1	14.3				+			+			A
232	1	14.3										A
237	1	14.3										A
238	1	14.3										A
240	1	14.3										A
56	2	28.6		A		+	+					S
9	0	.0										
13	1	14.3		A								
21	0	.0										
24	0	.0										
25	0	.0										
28	0	.0					+					
54	0	.0		-								
56	1	14.3		S			+					
60	0	.0										
63	0	.0										
64	1	14.3		S								
67	0	.0										
74	0	.0										
76	1	14.3					A					
87	0	.0										
92	1	14.3		A			+					
94	0	.0										
97	0	.0										
100	1	14.3		S								
101	1	14.3		A			+					
102	0	.0				+	+					
103	0	.0					+					
128	0	.0										
129	0	.0										
130	0	.0										
144	0	.0										
146	0	.0										
151	0	.0		+		+						
161	0	.0					+					
202	1	14.3		S								
207	1	14.3		S			+					
219	0	.0					+					
61	0	.0				+						
104	0	.0										

133	0	.0			+		
156	0	.0					
187	1	14.3	S				
163	1	14.3					A
66	2	28.6				A	S
52	1	14.3	-			A	
68	1	14.3				A	
119	2	28.6	A			A	
69	1	14.3				A	

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

In the data pattern table that follows which displays individual cases. the following symbols are used:

+. Extremely high value
-. Extremely low value
S. System-missing value
A. First type of user-missing value
B. Second type of user-missing value
C. Third type of user-missing value

Table 71. Missing Patterns for all participants (cases with missing values)

Case	# Missing	% Missing	Missing and Extreme Value Patterns[a]						
			MMSE pre-OP	Thrombosis	Leukocytes	CRP	SIRS or Sepsis	Blood Sample	Tel. MMSE post-OP
68	1	14.3						S	
69	1	14.3						S	
78	1	14.3						S	
79	1	14.3						S	
116	1	14.3						S	
48	1	14.3						A	
138	1	14.3						A	
183	1	14.3						A	
198	1	14.3				+		A	
211	1	14.3						A	
226	1	14.3		+	+			A	
232	1	14.3						A	
237	1	14.3						A	
238	1	14.3						A	
240	1	14.3						A	
163	1	14.3						A	
56	2	28.6			+	+		S	A
121	1	14.3							S
135	1	14.3							A
140	1	14.3							A
158	1	14.3							A
170	1	14.3							A
176	1	14.3							A
204	1	14.3				+			S
206	1	14.3							S
208	1	14.3							S
209	1	14.3							S
229	1	14.3							S
236	1	14.3							S
167	1	14.3							A
172	1	14.3							A
175	1	14.3	-						A
200	1	14.3							A
38	1	14.3							S
40	1	14.3							A
46	1	14.3							A
49	1	14.3							S
75	1	14.3							A
96	1	14.3			+				S
106	1	14.3							A
118	1	14.3	-						S
13	1	14.3							A
56	1	14.3				+			S
64	1	14.3							S
92	1	14.3				+			A
100	1	14.3							S
101	1	14.3				+			A
202	1	14.3							S
207	1	14.3				+			S
187	1	14.3							S
220	2	28.6			A				A
119	2	28.6					A		A
52	1	14.3					A		-
68	1	14.3					A		
69	1	14.3					A		
66	2	28.6					A	S	
110	1	14.3		+		A			
55	1	14.3				A			
181	1	14.3	-	+		S			
76	1	14.3				A			
148	1	14.3				S			

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

Table 72. Tabulated Patterns (Cases and variables are sorted on missing patterns).

Number of Cases	Missing Patterns[a]							Complete if ...[b]
	MMSE pre-OP	Thrombosis	Leukocytes	CRP	SIRS or Sepsis	Blood Sample	Tel. MMSE post-OP	
163								163
16						X		179
33							X	196
3					X			166
5				X				168

Patterns with less than 1% cases (2 or fewer) are not displayed.

a. Variables are sorted on missing patterns.

b. Number of complete cases if variables missing in that pattern (marked with X) are not used.

Listwise Statistics

Table 73. Listwise Means

Number of cases	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
163	27.17	18.97	7.7564	8.1135	237.40

Table 74. Listwise Covariances

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
MMSE pre-OP Total	7.843				
MMSE Post-OP	5.295	8.894			
Leukocytes	1.345	6.184	57.13437		
CRP	-5.751	-1.575	14.49420	317.61130	
Thrombosis	-6.708	13.037	29.04488	377.86249	4391.896

Table 75. Listwise Correlations

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
MMSE pre-OP Total	1				
MMSE Post-OP	.634	1			
Leukocytes	.064	.274	1		
CRP	-.115	-.030	.108	1	
Thrombosis	-.036	.066	.058	.320	1

EM Estimated Statistics

Table 76. EM Means[a]

MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
26.91	18.81	7.8085	8.8778	238.03

a. Little's MCAR test: Chi-Square = 12.143. DF = 11. Sig. = .353

Table 77. EM Covariances[a]

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
MMSE pre-OP Total	9.188				
MMSE Post-OP	6.148	9.261			
Leukocytes	1.472	5.295	46.81511		
CRP	-5.207	-1.530	14.78633	326.78903	
Thrombosis	-28.071	-3.473	20.84859	317.60409	4681.078

a. Little's MCAR test: Chi-Square = 12.143. DF = 11. Sig. = .353

Table 78. EM Correlations[a]

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
MMSE pre-OP Total	1				
Tel. MMSE post-OP	.666	1			
Leukocytes	.071	.254	1		
CRP	-.095	-.028	.120	1	
Thrombosis	-.135	-.017	.045	.257	1

a. Little's MCAR test: Chi-Square = 12.143. DF = 11. Sig. = .353

Regression Estimated Statistics

Table 79. Regression Means[a]

MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
27.07	18.88	7.9029	8.3270	239.38

a. Residual of a randomly chosen case is added to each estimate.

Table 80. Regression Covariances[a]

	MMSE pre-OP	Tel. MMSE post-OP	Leu-kocytes	CRP	Throm-bosis
MMSE pre-OP Total	8.751				
Tel. MMSE post-OP	6.114	9.594			
Leukocytes	1.416	4.387	47.80404		
CRP	-4.470	-1.897	13.31102	295.95898	
Thrombosis	-26.712	-14.703	52.17542	282.58961	4651.046

a. Residual of a randomly chosen case is added to each estimate.

Table 81.Regression Correlations[a]

	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	Thrombosis
MMSE Baseline	1				
Tel. MMSE Post-OP	.667	1			
Leukocytes	.069	.205	1		
CRP	-.088	-.036	.112	1	
Thrombosis	-.132	-.070	.111	.241	1

a. Residual of a randomly chosen case is added to each estimate.

Missing Values Analysis for participants with pre-OP Blood samples

Table 82. Univariate Statistic for participants with Blood Samples pre-OP

				Missing		No. of Extremes[b,c]	
	N	Mean	Std. Deviation	Count	Percent	Low	High
SIRS or Sepsis	167	.19	.395	5	2.9	.	.
MMSE pre-OP	170	26.96	2.901	2	1.2	1	0
Tel. MMSE post-OP	87	19.56	3.216	85	49.4	3	1
Leukocytes	169	7.8193	7.44458	3	1.7	0	4
CRP	166	9.2687	18.88294	6	3.5	0	18

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

*b. Number of cases outside the range (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

c. . indicates that the inter-quartile range (IQR) is zero.

Table 83. Summary of Estimated Means for participants with blood samples pre-OP[a]

	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
All Values	.19	26.96	19.56	7.8193	9.2687
EM	.19	26.96	19.46	7.8118	9.3161

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

Table 84. Summary of Estimated Standard Deviations for participants with blood samples pre-OP[a a]

	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
All Values	.395	2.901	3.216	7.44458	18.88294
EM	.395	2.901	3.202	7.44423	18.88946

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

Table 85. Separate Variance t Tests for participants with blood samples pre-OP[a a.b]

		SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
Tel. MMSE post-OP	t	-.1	.6	.	.2	-1.0
	df	164.6	162.9	.	95.6	160.2
	P(2-tail)	.911	.526	.	.857	.306
	# Present	85	87	87	87	84
	# Missing	82	83	0	82	82
	Mean(Present)	.19	27.10	19.56	7.9174	7.7786
	Mean(Missing)	.20	26.82	.	7.7154	10.7951

For each quantitative variable. pairs of groups are formed by indicator variables (present. missing).

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Indicator variables with less than 5% missing are not displayed.

Table 86. Tel. MMSE post-OP Percent Mismatch of Indicator Variables for participants with blood samples pre-OP[a] *.*[a.b.c]

	Tel. MMSE post-OP
Tel. MMSE post-OP	49.42

The diagonal elements are the percentages missing. and the off-diagonal elements are the mismatch percentages of indicator variables.

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Variables are sorted on missing patterns.

c. Indicator variables with less than 5% missing values are not displayed.

Table 87.Missing Value Codes in Pattern Tables[a]

	Pattern Codes
	A
SIRS or Sepsis	999
MMSE pre-OP Total	999
Tel. MMSE post-OP	999
Leukocytes	999.00
CRP	999.00

System missing values are marked with S.

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

In the data pattern table that follows which displays individual cases. the following symbols are used:

+. Extremely high value
-. Extremely low value
S. System-missing value
A. First type of user-missing value
B. Second type of user-missing value
C. Third type of user-missing value

Table 88. Data Patterns for participants with blood samples pre-OP[a] (all cases)[a]

			Missing and Extreme Value Patterns					Variable Values
				Tel. MMSE				
Case	# Missing	% Missing	SIRS or Sepsis	MMSE pre-OP	post-OP	Leukocytes	CRP	SIRS or Sepsis
95	5	100.0	S	S	S	S	S	.
177	5	100.0	S	S	S	S	S	.
1	1	20.0	-		S			0
6	1	20.0	-		S			0
7	0	.0	-					0
8	1	20.0	-		S			0
10	0	.0	-					0
12	1	20.0	-		S			0
14	1	20.0	-		S			0
16	0	.0	-					0
17	1	20.0	-		S			0
18	1	20.0	-		S			0
19	0	.0	-					0
22	0	.0	-				+	0
23	1	20.0	-		S			0
26	1	20.0	-		S			0
27	0	.0	-					0
31	1	20.0	-		S			0
32	0	.0	-					0
33	0	.0	-					0
34	0	.0	-					0
35	0	.0	-					0
37	0	.0	-				+	0
38	1	20.0	-		S			0
39	0	.0	-					0
40	1	20.0	-		S			0
42	0	.0	-					0
43	0	.0	-					0
44	0	.0	-					0
45	0	.0	-				+	0
46	1	20.0	-		S			0
49	1	20.0	-		S			0
50	0	.0	-					0
53	0	.0	-					0
55	2	40.0	-		S		A	0
57	0	.0	-					0
59	0	.0	-		-			0
71	0	.0	-					0

Table 88. Data Patterns for participants with blood samples pre-op[a] (all cases)[a] continued

			Missing and Extreme Value Patterns					Variable Values
Case	# Missing	% Missing	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP	SIRS or Sepsis
73	0	.0	-					0
75	1	20.0	-		S			0
77	0	.0	-					0
78	0	.0	-					0
79	0	.0	-					0
80	0	.0	-					0
81	0	.0	-					0
83	0	.0	-					0
84	0	.0	-					0
85	0	.0	-					0
86	0	.0	-					0
89	0	.0	-					0
91	0	.0	-					0
93	0	.0	-					0
96	1	20.0	-		S	+		0
98	0	.0	-					0
99	0	.0	-					0
105	0	.0	-				+	0
106	1	20.0	-		S			0
109	0	.0	-					0
110	1	20.0	-				A	0
111	0	.0	-					0
112	0	.0	-					0
113	1	20.0	-		S			0
114	1	20.0	-		S		+	0
115	1	20.0	-		S			0
116	1	20.0	-		S			0
117	0	.0	-					0
118	1	20.0	-	-	S			0
120	0	.0	-					0
121	1	20.0	-		S			0
122	1	20.0	-		S			0
124	1	20.0	-		S			0
125	1	20.0	-		S			0
126	1	20.0	-		S			0
131	1	20.0	-		S			0
135	1	20.0	-		S			0
139	0	.0	-					0
140	1	20.0	-		S			0
142	0	.0	-					0
143	0	.0	-					0
145	0	.0	-					0
147	0	.0	-					0
148	1	20.0	-				S	0
149	0	.0	-					0
150	0	.0	-					0
152	0	.0	-					0
153	0	.0	-					0
154	0	.0	-					0
155	0	.0	-					0
157	0	.0	-					0
158	1	20.0	-		S			0
162	0	.0	-					0
164	0	.0	-					0
165	0	.0	-					0
169	0	.0	-				+	0
170	1	20.0	-		S			0
176	1	20.0	-		S			0
178	1	20.0	-		S			0
179	0	.0	-					0
182	0	.0	-					0
184	0	.0	-					0
186	0	.0	-					0
188	0	.0	-					0
189	0	.0	-					0
191	1	20.0	-		S			0

192	0	.0	-				0
193	0	.0	-				0
194	0	.0	-				0
195	1	20.0	-	S		+	0
196	1	20.0	-	S			0
201	1	20.0	-	S			0
203	1	20.0	-	S			0
204	1	20.0	-	S		+	0
205	1	20.0	-	S			0
206	1	20.0	-	S			0
208	1	20.0	-	S			0
209	1	20.0	-	S			0
210	1	20.0	-	S	+		0
212	1	20.0	-	S			0
214	1	20.0	-	S			0
215	1	20.0	-	S		+	0
216	1	20.0	-	S			0
217	1	20.0	-	S			0
218	1	20.0	-	S			0
220	2	40.0	-	S	A		0
221	1	20.0	-	S			0
223	1	20.0	-	S			0
225	1	20.0	-	S			0
227	1	20.0	-	S			0
228	1	20.0	-	S			0
229	1	20.0	-	S			0
230	1	20.0	-	S			0
233	1	20.0	-	S			0
234	1	20.0	-	S			0
235	1	20.0	-	S			0
236	1	20.0	-	S			0
239	1	20.0	-	S			0
241	1	20.0	-	S			0
9	0	.0	+				1
13	1	20.0	+	S			1
21	1	20.0	+	S			1
24	1	20.0	+	S			1
25	0	.0	+				1
28	1	20.0	+	S		+	1
54	0	.0	+	-			1
56	1	20.0	+	S		+	1
60	0	.0	+				1
63	0	.0	+				1
64	1	20.0	+	S			1
67	0	.0	+				1
74	0	.0	+				1
76	1	20.0	+			A	1
87	0	.0	+				1
92	1	20.0	+	S		+	1
94	0	.0	+				1
97	1	20.0	+	S			1
100	1	20.0	+	S			1
101	1	20.0	+	S		+	1
102	0	.0	+		+	+	1
103	0	.0	+			+	1
128	1	20.0	+	S			1
129	1	20.0	+	S			1
130	0	.0	+				1
144	0	.0	+				1
146	0	.0	+				1
151	0	.0	+	+	+		1
161	1	20.0	+	S		+	1
202	1	20.0	+	S			1
207	1	20.0	+	S		+	1
219	1	20.0	+	S		+	1
52	1	20.0	A	-			999
68	1	20.0	A				999
119	2	40.0	A	S			999

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

Timing Blood Samples (Pre/Post OP) = Pre-OP

Table 89. Missing Patterns for participants with blood samples pre-OP (cases with missing values)[a]

			Missing and Extreme Value Patterns[b]					Variable Values
Case	# Missing	% Missing	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	CRP	Tel. MMSE post-OP	SIRS or Sepsis
1	1	20.0			-		S	0
6	1	20.0			-		S	0
8	1	20.0			-		S	0
12	1	20.0			-		S	0
14	1	20.0			-		S	0
17	1	20.0			-		S	0
18	1	20.0			-		S	0
23	1	20.0			-		S	0
26	1	20.0			-		S	0
31	1	20.0			-		S	0
38	1	20.0			-		S	0
40	1	20.0			-		S	0
46	1	20.0			-		S	0
49	1	20.0			-		S	0
75	1	20.0			-		S	0
96	1	20.0		+	-		S	0
106	1	20.0			-		S	0
113	1	20.0			-		S	0
114	1	20.0			-	+	S	0
115	1	20.0			-		S	0
116	1	20.0			-		S	0
118	1	20.0	-		-		S	0
121	1	20.0			-		S	0
122	1	20.0			-		S	0
124	1	20.0			-		S	0
125	1	20.0			-		S	0
126	1	20.0			-		S	0
131	1	20.0			-		S	0
135	1	20.0			-		S	0
140	1	20.0			-		S	0
158	1	20.0			-		S	0
170	1	20.0			-		S	0
176	1	20.0			-		S	0
178	1	20.0			-		S	0
191	1	20.0			-		S	0
195	1	20.0			-	+	S	0
196	1	20.0			-		S	0
201	1	20.0			-		S	0
203	1	20.0			-		S	0
204	1	20.0			-	+	S	0
205	1	20.0			-		S	0
206	1	20.0			-		S	0
208	1	20.0			-		S	0
209	1	20.0			-		S	0
210	1	20.0		+	-		S	0
212	1	20.0			-		S	0
214	1	20.0			-		S	0
215	1	20.0			-	+	S	0
216	1	20.0			-		S	0
217	1	20.0			-		S	0
218	1	20.0			-		S	0
221	1	20.0			-		S	0
223	1	20.0			-		S	0
225	1	20.0			-		S	0
227	1	20.0			-		S	0
228	1	20.0			-		S	0
229	1	20.0			-		S	0
230	1	20.0			-		S	0
233	1	20.0			-		S	0
234	1	20.0			-		S	0
235	1	20.0			-		S	0
236	1	20.0			-		S	0
239	1	20.0			-		S	0
241	1	20.0			-		S	0
13	1	20.0			+		S	1
21	1	20.0			+		S	1

24	1	20.0			+		S	1
28	1	20.0			+	+	S	1
56	1	20.0			+	+	S	1
64	1	20.0			+		S	1
92	1	20.0			+	+	S	1
97	1	20.0			+		S	1
100	1	20.0			+		S	1
101	1	20.0			+	+	S	1
128	1	20.0			+		S	1
129	1	20.0			+		S	1
161	1	20.0			+	+	S	1
202	1	20.0			+		S	1
207	1	20.0			+	+	S	1
219	1	20.0			+	+	S	1
220	2	40.0		A	-		S	0
55	2	40.0			-	A	S	0
76	1	20.0			+	A		1
110	1	20.0			-	A		0
148	1	20.0			-	S		0
52	1	20.0			A		-	999
68	1	20.0			A			999
119	2	40.0			A		S	999
177	5	100.0	S	S	S	S	S	.
95	5	100.0	S	S	S	S	S	.

*- indicates an extreme low value. while + indicates an extreme high value. The range used is (Q1 - 1.5*IQR. Q3 + 1.5*IQR).*

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Cases and variables are sorted on missing patterns.

Table 90.Tabulated Patterns for participants with blood samples pre-OP [a]

	Missing Patterns[b]						
Number of Cases	MMSE pre-OP	Leu-kocytes	SIRS or Sepsis	CRP	Tel. MMSE post-OP	Complete if ...[c]	SIRS or Sepsis
82						82	.18
80					X	162	.20
3				X		85	.33
2			X			84	.
2	X	X	X	X	X	172	.

Patterns with less than 1% cases (2 or fewer) are not displayed.[a]

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Variables are sorted on missing patterns.

c. Number of complete cases if variables missing in that pattern (marked with X) are not used.

d. Means at each unique pattern

EM Estimated statistics

Table 91. EM Means for participants with blood samples pre-OP[a.b]

SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
.19	26.96	19.46	7.8118	9.3161

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

Little's MCAR test: Chi-Square = 15.859. DF = 21. Sig. = .

.778

Table 92.EM Covariances for participants with blood samples pre-OP [a.b]

	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
SIRS or Sepsis	.156				
MMSE pre-OP	-.051	8.413			
Tel. MMSE post-OP	-.090	5.880	10.253		
Leukocytes	.539	1.426	6.206	55.41658	
CRP	1.717	-5.200	-3.323	15.33105	356.81181

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Little's MCAR test: Chi-Square = 15.859. DF = 21. Sig. = .778

Table 93. EM Correlations for participants with blood samples pre-OP [a.b]

	SIRS or Sepsis	MMSE pre-OP	Tel. MMSE post-OP	Leukocytes	CRP
SIRS or Sepsis	1				
MMSE pre-OP	-.045	1			
Tel. MMSE post-OP	-.071	.633	1		
Leukocytes	.184	.066	.260	1	
CRP	.230	-.095	-.055	.109	1

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Little's MCAR test: Chi-Square = 15.859. DF = 21. Sig. = .778

Checking for Outliers: Boxplots

Figure 1. Boxplot of MMSE pre-OP for participants with blood samples before OP

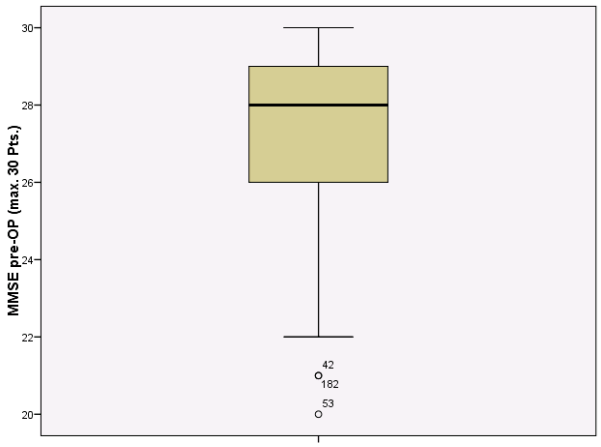


Figure 2. Boxplot of telephone MMSE post-OP for participants with blood samples before OP (max. 22Pts.)

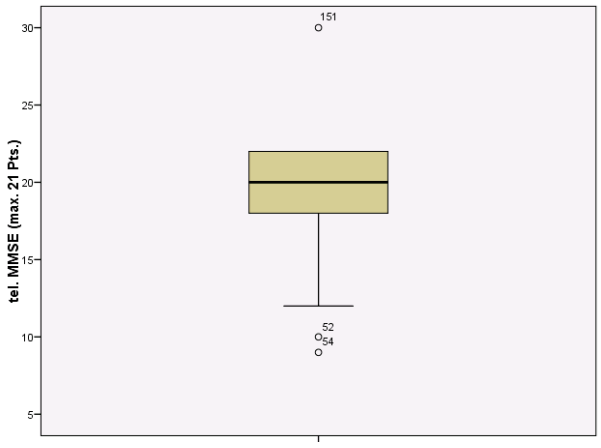


Figure 3. Boxplot of C-reactive Protein (CRP) for participants with blood samples before OP-

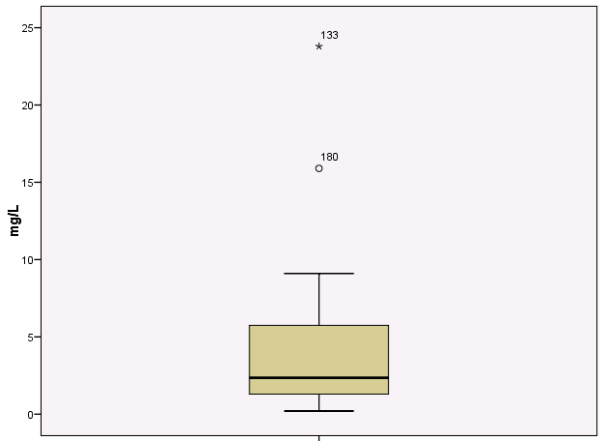
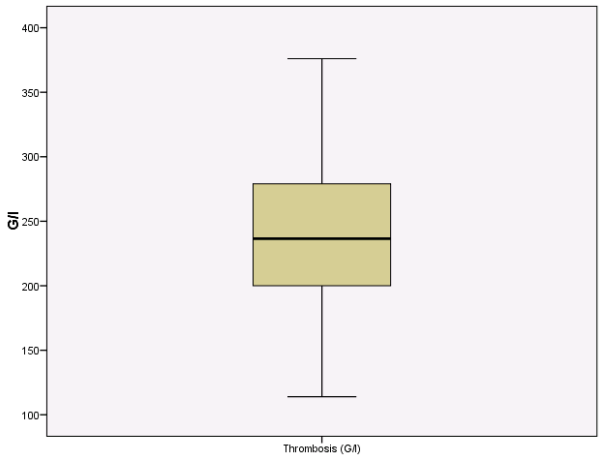


Figure 4. Boxplot of procalcitonin (PCT) for participants with blood samples before OP



Data Screening

Testing of Normality Raw Values

Table 94. Testing of Normality for participants with pre-OP Blood Samples [a]

	Kolmogorov-Smirnov[b]			Shapiro-Wilk		
	Sta-tistic	df	Sig.	Sta-tistic	df	Sig.
MMSE pre-OP (max. 30 Pts.)	.196	84	.000	.876	84	**.000**
Tel. MMSE Total post-OP (max. 22 Pts)	.219	84	.000	.835	84	**.000**
Leukocytes (G/l)	.385	84	.000	.205	84	**.000**
C-Reactive Protein	.366	84	.000	.409	84	**.000**
Thrombosis (G/l)	.083	84	.200*	.937	84	**.000**

*. This is a lower bound of the true significance.

a. Timing Blood Samples (Pre/Post OP) = Pre-OP

b. Lilliefors Significance Correction

Figure 5. Normal Q-Q Plot of MMSE pre-OP (maximum 30 Pts.) for those with blood samples pre-OP

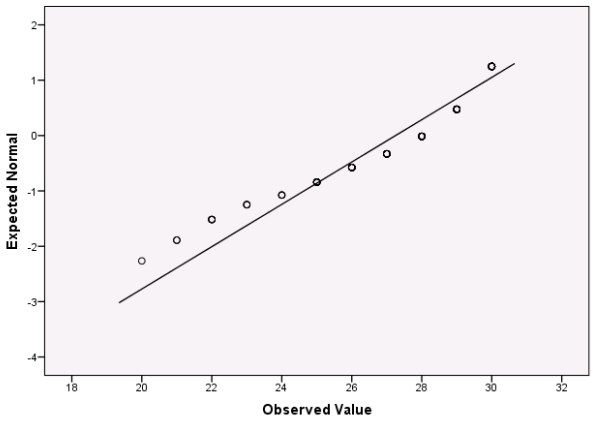


Figure 6. Detrended Normal Q-Q Plot of MMSE pre-OP (maximum 30 Pts.) for those with blood samples pre-OP

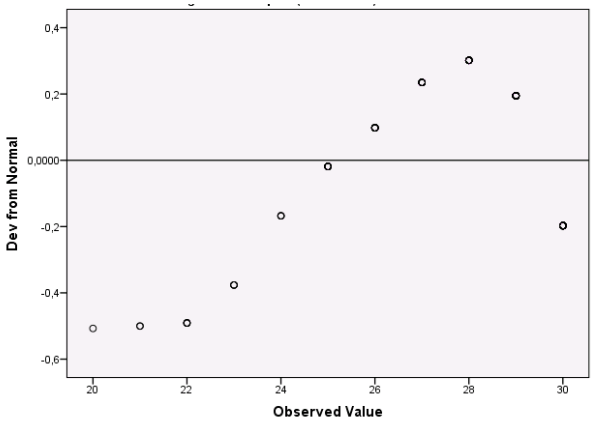


Figure 7. Normal Q-Q Plot of telephone MMSE (max. 22 Pts.)for those with blood samples pre-OP

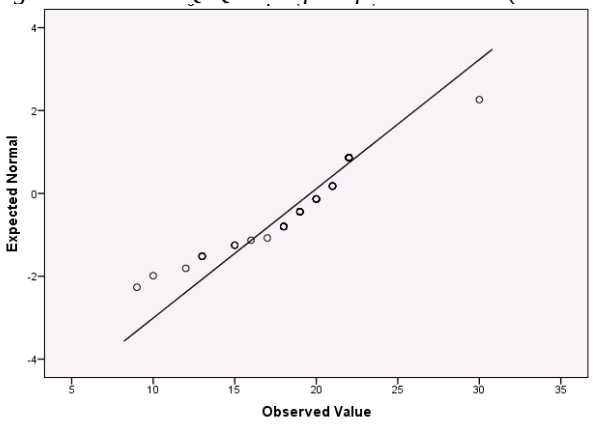


Figure 8. Detrended Normal Q-Q Plot of telephone MMSE (max. 22 Pts.) for those with blood samples pre-OP

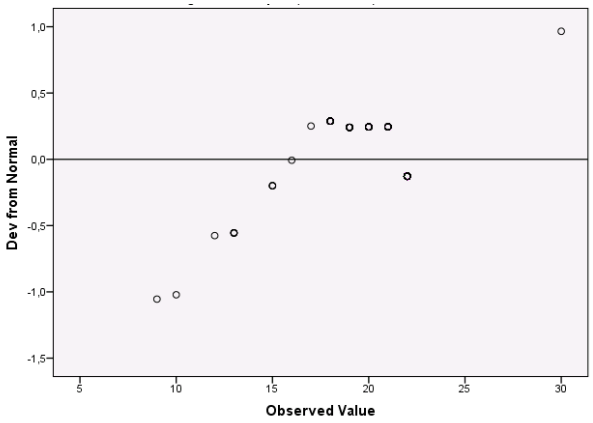
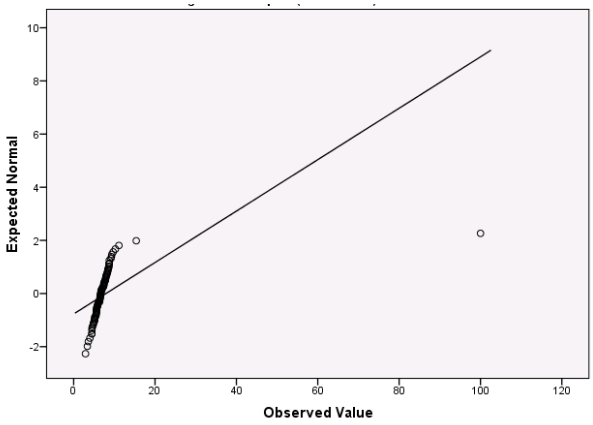


Figure 9. Normal Q-Q Plot of leukocytes for those with blood samples pre-OP



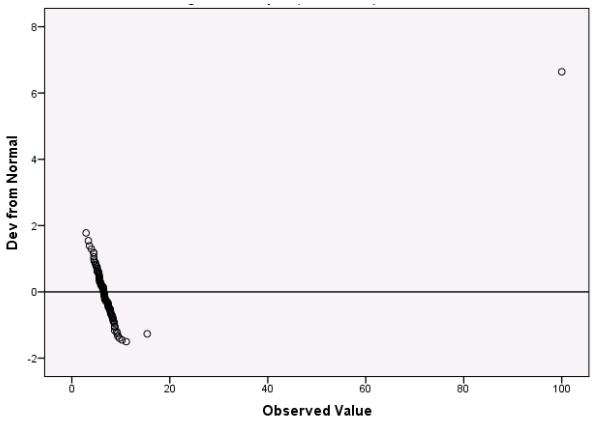


Figure 10. Detrended Normal Q-Q Plot of leukocytes for those with blood samples pre-OP

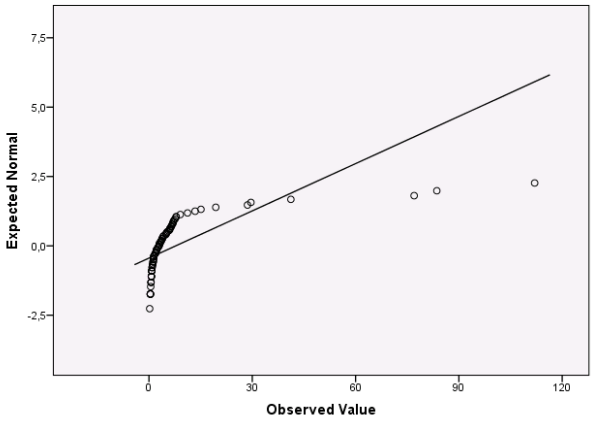


Figure 11. Normal Q-Q Plot of C-Reactive Protein (CRP) for those with blood samples pre-OP

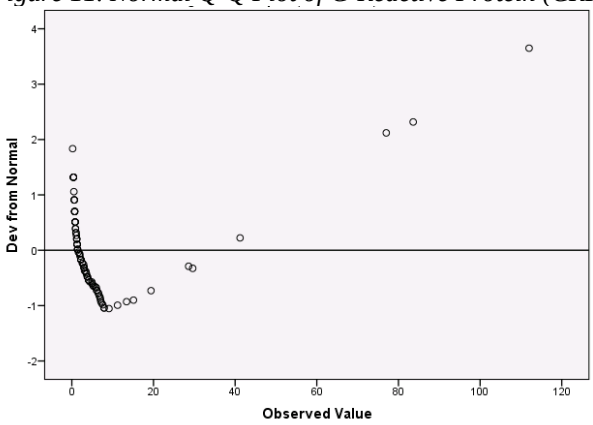


Figure 12. Detrended Normal Q-Q Plot of C-Reactive Protein (CRP) for those with blood samples pre-OP

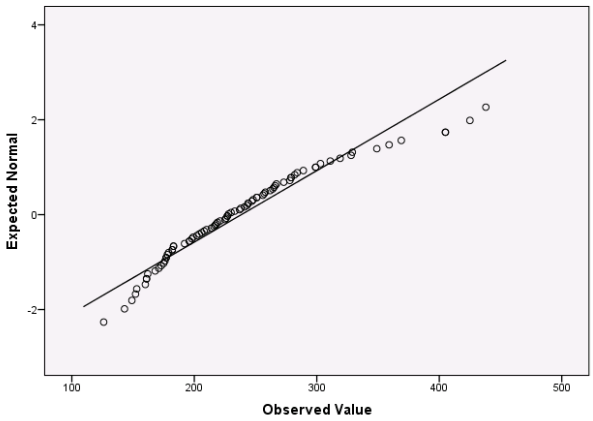
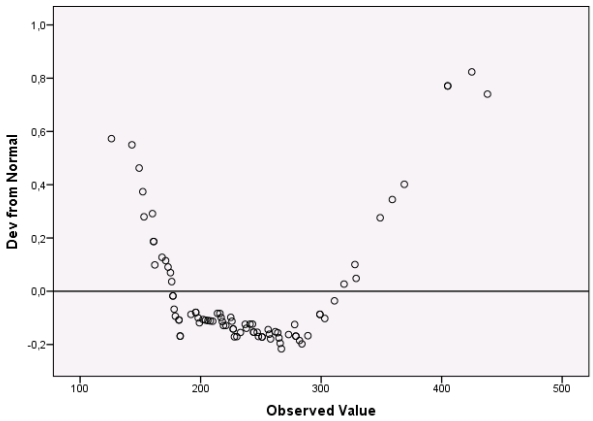


Figure 13. Normal Q-Q Plot of thrombocyte levels for those with blood samples pre-OP

Figure 14. Detrended Normal Q-Q Plot of thrombocyte levels for those with blood samples pre-OP



Appendix E Regression Analyses Study 3

Table 1. Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PreOP C-Reactive Pro-teinb	.	Enter
2	PostOP Peak C-Reactive Proteinb	.	Enter

a. Dependent Variable: VLMT Learning Trials 1-5

b. All requested variables entered.

Table 2. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.161[a]	.026	-.008	10.438
2	.208[b]	.043	-.025	10.529

a. Predictors: (Constant), PreOP C-Reactive Protein

b. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 3. ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	84.458	1	84.458	.775	.386[b]
	Residual	3159.413	29	108.945		
	Total	3243.871	30			
2	Regression	140.074	2	70.037	.632	.539[c]
	Residual	3103.797	28	110.850		
	Total	3243.871	30			

a. Dependent Variable: VLMT Learning Trials 1-5

b. Predictors: (Constant), PreOP C-Reactive Protein

c. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 4. Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	42.724	2.658		16.071	.000
	PreOP C-Reactive Protein	-.555	.630	-.161	-.880	.386
2	(Constant)	38.827	6.120		6.344	.000
	PreOP C-Reactive Protein	-.557	.636	-.162	-.876	.389
	PostOP Peak C-Reactive Protein	.026	.036	.131	.708	.485

a. Dependent Variable: VLMT Learning Trials 1-5

Table 5. Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics
						Tolerance
1	PostOP Peak C-Reactive Protein	.131[b]	.708	.485	.133	1.000
	CRP Rise	.131[b]	.709	.484	.133	.997
2	CRP Rise	20.038[c]	.216	.831	.042	4.112E-6

a. Dependent Variable: VLMT Learning Trials 1-5

b. Predictors in the Model: (Constant), PreOP C-Reactive Protein

c. Predictors in the Model: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 6. Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PreOP C-Reactive Proteinb	.	Enter
2	PostOP Peak C-Reactive Proteinb	.	Enter

a. Dependent Variable: VLMT Trial 1

b. All requested variables entered.

Table 7. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.040[a]	.002	-.033	1.633
2	.134[b]	.018	-.052	1.648

a. Predictors: (Constant), PreOP C-Reactive Protein

b. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 8. ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	.121	1	.121	.046	.833b
	Residual	77.298	29	2.665		
	Total	77.419	30			
2	Regression	1.384	2	.692	.255	.777c
	Residual	76.035	28	2.716		
	Total	77.419	30			

a. Dependent Variable: VLMT Trial 1

b. Predictors: (Constant), PreOP C-Reactive Protein

c. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 9. Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	5.163	.416		12.416	.000
	PreOP C-Reactive Protein	.021	.099	.040	.213	.833
2	(Constant)	4.576	.958		4.777	.000
	PreOP C-Reactive Protein	.021	.100	.039	.209	.836
	PostOP Peak C-Reactive Protein	.004	.006	.128	.682	.501

a. Dependent Variable: VLMT Trial 1

Table 10. Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics
						Tolerance
1	PostOP Peak C-Reactive Protein	.128[b]	.682	.501	.128	1.000
	CRP Rise	.128[b]	.682	.501	.128	.997
2	CRP Rise	-13.596[c]	-.145	.886	-.028	4.112E-6

a. Dependent Variable: VLMT Trial 1

b. Predictors in the Model: (Constant), PreOP C-Reactive Protein

c. Predictors in the Model: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 11. Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PreOP C-Reactive Protein[b]	.	Enter
2	PostOP Peak C-Reactive Protein[b]	.	Enter

a. Dependent Variable: VLMT Trial 6 Correct

b. All requested variables entered.

Table 12. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.254[a]	.064	.032	3.429
2	.254[b]	.064	-.002	3.489

a. Predictors: (Constant), PreOP C-Reactive Protein

b. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 13. ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	23.449	1	23.449	1.995	.169[b]
	Residual	340.938	29	11.756		
	Total	364.387	30			
2	Regression	23.493	2	11.747	.965	.393[c]
	Residual	340.894	28	12.175		
	Total	364.387	30			

a. Dependent Variable: VLMT Trial 6 Correct

b. Predictors: (Constant), PreOP C-Reactive Protein

c. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 14. Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	7.584	.873		8.685	.000
	PreOP C-Reactive Protein	-.292	.207	-.254	-1.412	.169
2	(Constant)	7.693	2.028		3.793	.001
	PreOP C-Reactive Protein	-.292	.211	-.254	-1.388	.176
	PostOP Peak C-Reactive Protein	-.001	.012	-.011	-.060	.953

a. Dependent Variable: VLMT Trial 6 Correct

Table 15. Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics
						Tolerance
1	PostOP Peak C-Reactive Protein	-.011[b]	-.060	.953	-.011	1.000
	CRP Rise	-.011[b]	-.060	.953	-.011	.997
2	CRP Rise	12.314[c]	.134	.894	.026	4.112E-6

a. Dependent Variable: VLMT Trial 6 Correct

b. Predictors in the Model: (Constant), PreOP C-Reactive Protein

c. Predictors in the Model: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 16. Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PreOP C-Reactive Protein[b]	.	Enter
2	PostOP Peak C-Reactive Protein[b]	.	Enter

a. Dependent Variable: VLMT Trial 7 Correct

b. All requested variables entered.

Table 17. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.129[a]	.017	-.017	3.402
2	.159[b]	.025	-.044	3.447

a. Predictors: (Constant), PreOP C-Reactive Protein

b. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 18. ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5.699	1	5.699	.492	.488[b]
	Residual	335.720	29	11.577		
	Total	341.419	30			
2	Regression	8.644	2	4.322	.364	.698[c]
	Residual	332.775	28	11.885		
	Total	341.419	30			

a. Dependent Variable: VLMT Trial 7 Correct

b. Predictors: (Constant), PreOP C-Reactive Protein

c. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 19. Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	7.657	.867		8.836	.000
	PreOP C-Reactive Protein	-.144	.205	-.129	-.702	.488
2	(Constant)	6.760	2.004		3.373	.002
	PreOP C-Reactive Protein	-.145	.208	-.130	-.695	.493
	PostOP Peak C-Reactive Protein	.006	.012	.093	.498	.623

a. Dependent Variable: VLMT Trial 7 Correct

Table 20. Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	PostOP Peak C-Reactive Protein	.093[b]	.498	.623	.094	1.000
	CRP Rise	.093[b]	.498	.622	.094	.997
2	CRP Rise	23.412[c]	.250	.804	.048	4.112E-6

a. Dependent Variable: VLMT Trial 7 Correct

b. Predictors in the Model: (Constant), PreOP C-Reactive Protein

c. Predictors in the Model: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 21. Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	PreOP C-Reactive Protein[b]	.	Enter
2	PostOP Peak C-Reactive Protein[b]	.	Enter

a. Dependent Variable: VLMT Recognition Correct

b. All requested variables entered.

Table 22. Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.117[a]	.014	-.020	2.317
2	.185[b]	.034	-.035	2.334

a. Predictors: (Constant), PreOP C-Reactive Protein

b. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 23. ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2.168	1	2.168	.404	.530[b]
	Residual	155.703	29	5.369		
	Total	157.871	30			
2	Regression	5.381	2	2.690	.494	.615[c]
	Residual	152.490	28	5.446		
	Total	157.871	30			

a. Dependent Variable: VLMT Recognition Correct

b. Predictors: (Constant), PreOP C-Reactive Protein

c. Predictors: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein

Table 24. Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	12.330	.590		20.893	.000
	PreOP C-Reactive Protein	-.089	.140	-.117	-.635	.530
2	(Constant)	11.394	1.357		8.399	.000
	PreOP C-Reactive Protein	-.089	.141	-.118	-.634	.531
	PostOP Peak C-Reactive Protein	.006	.008	.143	.768	.449

a. Dependent Variable: VLMT Recognition Correct

Table 25. Excluded Variables[a]

Model		Beta In	t	Sig.	Partial Correlation	Collinearity Statistics Tolerance
1	*PostOP Peak C-Reactive Protein*	*.143[b]*	*.768*	*.449*	*.144*	*1.000*
	CRP Rise	*.143[b]*	*.771*	*.447*	*.144*	*.997*
2	*CRP Rise*	*119.377[c]*	*1.321*	*.198*	*.246*	*4.112E-6*

a. Dependent Variable: VLMT Recognition Correct

b. Predictors in the Model: (Constant), PreOP C-Reactive Protein

c. Predictors in the Model: (Constant), PreOP C-Reactive Protein, PostOP Peak C-Reactive Protein