Inflammatory profile in schizophrenia and bipolar disorder.

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Relation to affective state.

A PhD thesis

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Content

1 Acknowledgements

The studies reported in this thesis were carried out during the years 2007-11 at Østfold Hospital, Division of Psychiatry, Oslo University Hospital, Division of Mental Health and Addiction and at Institute of Clinical Medicine, University of Oslo. The study was part of the Thematically Organized Psychosis Research (TOP) Study, which is organized at Section for Psychosis Research, Oslo University Hospital and was funded by a grant from the Helse Øst. Analyses of Immunological blood samples were performed at Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital, Rikshospitalet, Oslo.

Several persons have contributed to the study.

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2 Summary of the thesis

Background: Schizophrenia and bipolar disorder are debilitating disorders. In addition to classic psychotic and mood symptoms, frequency of cognitive disturbances and mortality from cardiovascular disease are high. Inflammation has been associated with both cognitive disturbances and cardiovascular disease. Recent studies have indicated increased inflammation in patients with severe mental disorders. However, these studies are small and have a limited number of inflammatory markers. This makes it difficult to draw any conclusions about the mechanisms involved. No studies have investigated if inflammatory disturbances differ between schizophrenia and bipolar disorder. Inflammation has been associated with depression and mania, but it is still unclear how it relates to mood symptoms and affective states.

Aims: The aims were to determine if patients with severe mental disorder have high levels of inflammation, if they have a specific inflammatory profile, if inflammatory disturbances differ between schizophrenia and bipolar disorder patients, and if inflammatory profile is associated with mood symptoms or affective state.

Methods: 312 patients from a catchment area were included together with 239 healthy controls. Patients were diagnosed according to DSM-V, and degree of depression and mania was assessed with standard instruments.

Four general inflammatory markers were measured: Tumor necrosis factor receptor 1 (TNF-R1), Interleukin 1 receptor antagonist (IL-1Ra), Interleukin 6 (IL-6) and high-sensitivity CRP (hs-CRP). Three specific markers were measured: The platelet related inflammatory marker CD40L ligand (sCD40L), the endothelial related marker von Willebrand factor (vWf) and the calcium related inflammatory marker Osteoprotegerin (OPG). Routine biochemical blood tests and clinical characteristics, which could confound associations, were also assessed.

Results: Patients had a similar immune profile with highly significant increase of TNF-R1, vWf and OPG ($p<0.000002$, $p<0.000002$, and $p=0.01$ respectively). The results were significant also after control for confounding factors. Contrary to expectations, depressed bipolar disorder patients had the lowest levels of inflammation and manic patients had the highest.

Degree of depressive mood was also inversely correlated with inflammation, which was significant for OPG ($p=0.0003$), IL-1Ra ($p=0.001$) and IL-6 ($p= 0.002$). Patients in manic state had significantly higher levels of OPG, vWf, IL-1Ra and sTNF-R1.

There were no associations between mood and inflammation in schizophrenia.

Discussion: The study indicated that the general inflammatory marker TN-R1, as well as endothelial and calcium related inflammation may play a role in severe mental illness pathology. TNF-R1 has been found to be involved in neuronal plasticity, and related to cognitive dysfunction, which is an important clinical characteristic of the disorders. The results are also in line with recent findings that endothelial dysfunction and calcium metabolism are involved in the pathology. Furthermore, OPG and vWf are risk factors of cardiovascular disease and the high levels in patients may be related to their elevated mortality rates.

It has been fairly well documented that inflammation induces typical sickness behavior, with reduced energy, increased sleep and depressive mood. Therefore, it was unexpected that inflammation was increased in the manic state. This suggests that there may be other inflammatory mechanisms involved.

Conclusions: Both bipolar disorder and schizophrenia show increased TNF-R1, OPG and vWf. This immune profile suggests inflammatory disturbances related to neuroplasticity, endothelial function and calcium regulation.

In bipolar disorder patients, elevated mood is characterized by high levels of inflammation, while depressed mood is characterized by low. This suggests that inflammatory disturbances may be involved with core psychopathology of bipolar disorder.

The study supports that inflammatory disturbances are of importance in severe mental disorders.

3 List of studies

I. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, Agartz I, Ueland T, Andreassen OA. *Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor*. Bipolar Disord 2009 11:726-734.

II. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, Agartz I, Ueland T, Andreassen OA, *Osteoprotegerin levels in patients with severe mental disorders*. J Psychiatry Neurosci, 2010. 35(5): 304-10.

III. Hope S, Dieseth I , Agartz I, Steen NE, Ueland T, Melle I, Aukrust P, Andreassen OA. *Mood states are associated with markers of inflammation and immune activation in bipolar disorder but not in schizophrenia*. J Psychiatr Res., Epub ahead of print, 2011.

4 General introduction

4.1 The relationship between psyche and soma

The relationship between body and soul has been discussed since antiguity. After many years of research modern biomedicine established that mental stress increases the risk of somatic illness. A putative mechanism is that mental stress suppresses the immune system, which leads to impaired defense mechanisms and increased risk of diseases. The association between psychological and somatic disease is seen in patients with severe mental disorders, as they are highly vulnerable to mental stress and have elevated risk of most diseases. Recent research has also suggested that they have immunological disturbances.

However, it is unknown if they have any specific immune related disturbances making them more prone to cardiovascular diseases than for instance metastatic cancer. Recently an intriguing link between the immune system and mental function has been found. It was discovered that immune molecules are directly involved in an important brain function, memory consolidations. Patients with severe mental disorders have reduced memory functioning, and thus one may wonder if both their risk of medical disease and of brain function disturbances are immune related.

Bipolar disorder (BP) and schizophrenia (SCH) have several similarities. Patients with both disorders may have psychotic symptoms, mood disturbances, cognitive disturbances and high risk of medical diseases. Therefore, it is possible that they also may have the same kind of immune disturbances, but this has not yet been investigated.

A typical immune activation induces symptoms commonly seen in sickness, as increased need for sleep, impaired appetite and reduced energy. These symptoms are similar to symptoms seen in depression. Manic patients, on the contrary, often have opposite symptoms from those induced by typical immune activation. Do depressed patients have opposite kinds of immune disturbances than the manic? This is still unknown.

There are still many unanswered questions regarding the interaction between psychological and medical disease. Increased understanding of the pathological mechanisms involved could lead to better treatment for both mental and physical diseases.

To contribute to such increased understanding was the motivation for conducting the present work.

4.2 Schizophrenia

4.2.1 Diagnostic definition

There are no pathognomonic signs for SCH. The disorder is defined by a set of symptoms which are described in the Diagnostic and Statistical Manual for Mental Disorders (DSM) [1]. To fulfill the diagnostic criteria patients must have had a minimum set of characteristic psychotic symptoms (delusions, hallucinations, thought disorders) for at least one month, as well as some symptoms of the disorder lasting for at least 6 months. A marked dysfunction must also be present. If affective episodes and psychotic symptoms occur simultaneously, the psychotic symptoms must be present at least 2 weeks in the absence of prominent mood symptoms. Otherwise, the disorder is classified as schizoaffective disorder. If the duration of symptoms is shorter than 6 months, the disorder is classified as schizophreniform disorder. Schizophreniform disorder, schizoaffective disorder and schizophrenia are called "schizophrenia spectrum disorders".

4.2.2 Prevalence and risk factors

The prevalence of SCH is estimated to be about 0.5 - 1.0 %, being slightly more frequent in the male gender [2]. The prevalence is more geographically varied than previously assumed, and is higher in urban regions and in the northern latitudes. Migration and having a father of old age are risk factors [2, 3], as well as obstetric complications and prenatal infections [2]. Drug abuse, especially intoxication with cannabis, is associated with elevated frequency of developing schizophrenia [2]. There are also some studies indicating that social stress and abuse may precipitate psychosis [2]. In addition to these environmental risk factors, SCH has a high heritability with heritable estimates of 0.6-0.8 [4].The concordance rate for monozygotic twins is approximately 40-50%, indicating that environmental factors are also important [2]. Recently specific genetic risk factors have been identified, as further described in "3.2.3 Genetic mechanisms".

4.2.3 Disease characteristics

Disease course: Age at onset is usually in adolescence or young adulthood, but patients may also get the disorder in childhood or later in adulthood [2]. The course of the disorders differs among patients. Some get a chronic disease, never obtaining remission, while others achieve complete

remission and do not relapse. A substantial group has a relapsing and remitting disease course [5].

Many patients report reduced quality of life and many patients are depressed [2]. Also mania like symptoms as grandiosity, agitation and irritability are frequent [6]. According to nationwide Swedish register studies, 6% of those who had been admitted to hospital twice, commit suicide. The risk of violent crimes is also increased [7]. Those who have poor premorbid function and a long duration of untreated psychosis tend to have poorer treatment outcome [2]. Many patients do not fully recover and need lifelong treatment and social security services [8].

Cognitive impairments: Many patients have slight cognitive deficits, and cognitive impairment is one of the most important factors for outcome [9, 10]. The main domains affected are executive function, attention and memory. The patients may have problems with complicated reasoning, forgetfulness, learning disabilities and concentration difficulties. A decline in cognitive function mainly occurs in the period of illness onset, although there are also some indications that the cognitive impairment progress after illness onset [2, 11].

Somatic disease: The patients have high mortality, and the lifetime expectancy is reduced by approximately 20 years [12]. The disease has high comorbidity with many medical diseases, especially of cardiovascular disease [13]. The patients have also been found to have elevated frequency of diabetes [14], chronic obstructive lung disease [14] and autoimmune diseases [15]. The causes of the large excess in mortality rates are uncertain. It has been assumed that poor life style habits as little physical activity and high frequency of smoking, as well as side effects of medication may be at least partly responsible. Another reason may be that patients with severe mental disorders receive poorer somatic health care than the population in general [16, 17].

4.2.4 Treatment

Biological treatments: The main medication is antipsychotic agents targeting dopamine neurotransmission. They are efficient in 60-80 %of the patients and have a “Number Needed to Treat “of 2-5 [18]. They are mainly effective on positive psychotic symptoms, while the effects on negative symptoms and cognitive dysfunction are small, if any at all [2]. The first types of antipsychotics that were developed in the 1950s have a high selectivity for blocking dopamine D2 receptors. They do relatively often induce motor side effects, while the second generation of

antipsychotics tends to induce less troublesome side effects of this type due to more balanced blocking of dopamine and serotonin receptors [2]. The second-generation antipsychotics have however, a tendency to induce serious metabolic side effects. The use of the highly effective clozapine, is also limited by its tendency to induce agranulocytosis [2, 19].

Psychosocial treatments: Treatment regimens also include psychotherapy, psychoeducative family interventions, psychosocial support, and vocational rehabilitation [2]. Due to a negative impact of long duration of untreated psychosis, treatment programs for early intervention have been developed [2].

4.2.5 Pathological mechanisms

Genetic mechanisms: Two years ago, three large whole genome studies from several countries found that the five top susceptibility markers for SCH were located in a genetic region called the Major Histocompability Complex [20]. As explained in section 3.4.2, this region contains important immune related genes. One of the markers that have been replicated also in later studies is located near the gene TCF4. The highest expression of this gene is in the brain and in the spleen [21]. Its function is not fully known. In the brain it has been found important for cognitive function [22], and in the immune system for the maturing of immune cells [21]. NOTCH 4 is another of the top susceptibility genes in the MHC region [20]. The role of this gene in the brain is also largely unknown, but it is has been found important for endothelial function and vascular pathology [23].

In addition, genes outside the MHC region have been found to confer risk. Genes related to calcium and sodium channels as CACNA1c, Neurogranin, and ANK3 are among those most replicated [20, 24]. CACNA1c encodes a calcium channel, Neurogranin is involved with long term memory formation [20], while ANK3 is involved with regulation of sodium channels in neurons [25]. The gene ZNF804a also confers risk of SCH. The risk-associated variant has been associated with somewhat better cognitive function in patients, but how it relates to pathology is still unclear [26].

Two other recently discovered risk genes, CSMD1 1 and 2, have been associated with memory formation and with the innate immune system/complement (see 3.4.1) [27]. Genetic parts encoding Human endogenous retrovirus (HERV-W) have also been implicated in the pathology of SCH. HERVs are not encoded by ordinary genes, but are encoded by so-called “junk DNA”,

that previously were thought to be without any function. Proteins encoded by HERV-W have been found elevated in the serum of SCH [28].

Disturbed neurotransmission: Excess dopamine neurotransmission has been regarded as a central pathological mechanism in SCH and a range of dopaminergic abnormalities has been found. They have been related to limbic structures and affect regulation, as well as to cognition motivation and reward [2]. However, in a substantial part of patients, blocking dopamine with antipsychotics does not lead to remission, and current evidence does not support that excess dopamine transmission is the primary cause of the disease [2]. It has been suggested that patients may have an underlying glutamatergic abnormality. Excess glutamate may both influence dopamine and induce SCH-like symptoms. Glutamate may also be toxic to neurons and cause neurodegeneration when in excess, leading to the morphological changes found in patients. An important pathological mechanism of glutamate is suggested to be through impact on calcium and NMDA receptors [2, 29].

Neuronal substrates: Reduced brain volumes in specific areas and enlarged ventricles is one of the best documented pathological findings in SCH [2]. Large reviews of the imaging studies suggest that there are thinner frontal and temporal cortex and reduced subcortical structures, for example of the hippocampus [2]. New research indicates that these morphological changes are associated with poorer cognitive dysfunction [30, 31]. Most of these changes are present already at onset of disease [2], but studies have also reported that that the morphological changes are increasing [2]. According to a recent meta-analysis, the ventricular enlargements progress after onset of the disorder [32].

Immune hypothesis of schizophrenia: Several authors have proposed that immune related disturbances are central causes of SCH. These immune hypotheses are not contradictory to the previously mentioned theories about pathology, but provide some novel explanations for how immune related gene-environmental interactions may influence pathology [33-36]. Immune related genes are among the main genetic risk factors (as described in 3.2.3) and infections are among the main environmental risk factors. A large study including 1.2 million children, found that infections with two pathogens during pregnancy increased risk of SCH; Cytoplasma virus (CMV) and mumps [37]. Two other large studies found the herpes simplex virus 2 (HSV2)

[38]and toxoplasma gondii [39, 40] during pregnancy conferred elevated risk. In addition, high levels of cytomegalovirus, coronavirus and measles have been found in first episode patients [41-44]. According to a meta-analysis SCH patients have higher levels of toxoplasma antibodies [45]. Patients do not have higher titers of Herpes simplex 1 (HSV1), but still, this is the only pathogen that has been associated with poorer cognitive function in patients. Six studies have found that those who have antibodies of HSV1 in their serum have poorer cognitive function [46-51]. This suggests that there may be an interaction between herpes virus and pathological mechanisms causing cognitive disturbances, which are key characteristics of SCH.

4.3 Bipolar disorder

4.3.1 Diagnostic definitions

The diagnosis of bipolar disorder (BP) is based on the presence of a certain set of symptoms [1], of which none is pathognomonic. To fulfill the diagnostic criteria patients must have had at least one major depressive episode and one episode of mania or hypomania. Whether they have had a manic episode or only a hypomanic, determines whether the diagnosis is classified as bipolar I disorder (BPI) or bipolar II disorder (BPII), respectively. Mania and hypomania have the same main symptoms, although mania is a more severe condition than hypomania. A manic episode is defined by a distinct period of elevated, expansive or irritable mood. It is accompanied by a set of related signs or symptoms as increased self-esteem, energy, and involvement in pleasure-related activities. The need for sleep and rest is reduced. In contrast to hypomania, mania implies marked impairment in social functioning and may be characterized by the presence of psychosis [1].

A major depressive episode is characterized by a distinct period of at least two weeks duration with depressed mood or anhedonia, accompanied by symptoms as disturbance of sleep and appetite, reduced self-esteem and energy, agitation/retardation or suicide thoughts, as well as a functional decline [1].

Between affective episodes, patients may be well functioning without symptoms.

4.3.2 Prevalence and risk factors

The prevalence of BP varies across studies, but approximately equals SCH. Prevalence has been estimated to 0.6% for BP I, 1.4% for BP II and 2.6% for bipolar spectrum disorders [2, 52]. The

prevalence is equally high in men and women [2]. Bipolar disorder has high hereditability, estimated to 0, 6-0.8 [2]. Specific genetic risk markers are described in section 3.3.5. Pre- and perinatal complications [53], being born during winter or spring [54], head injuries [55], living in an urban district [56]and stressful life events [54] are also associated with increased risk. In contrast to SCH, low premorbid IQ is not associated with elevated risk [57]. Whether the risk of BP increases after infections in fetal life or in later life is not known.

4.3.3 Disease characteristics

Disease course: The onset is usually in adolescence and young adulthood [2]. The duration of episodes varies a lot, but most episodes last between two to seven months [58], with depressive episodes lasting approximately twice as long as the manic episodes [59]. Many patients experience psychotic symptoms [2], and tend to have cognitive impairments resembling those seen in SCH [60]. Patients report reduced quality of life, high rates of alcohol and drug abuse [61, 62], and have highly increased risk of suicide [63].

Compared to patients with unipolar depression, patients with bipolar depression have a greater number of short depressive episodes, are more often psychotic, have larger diurnal mood variation and more often hypersomnia [64]. The disorder tends to have an accelerating rate of affective episodes and progressive reduction in periods with neutral mood [2]. Fifteen years after onset, about one third of patients have persistent unremitting symptoms [2].

Somatic disease and mortality: BP patients have an elevated risk of cardiovascular diseases. The risk seems to be especially pronounced in mania [65, 66]. A large study also reported that they have an increased frequency of 41 out of 44 diseases investigated [67], including hypertension, stroke, coagulopathies, headache, neurological diseases, pulmonary disease, AIDS, and cancer. One of the few diseases they have reduced risk of is the immune related cancer lymphoma [67]. Their life time expectancy is reduced by than approximately 10 years [68].

Cognitive function: According to a prospective study including 50.000 men, poor premorbid IQ does not increase risk of BP, in contrast to SCH [57, 69]. After disease onset, patients do have cognitive disturbances, which has been found to be present also in euthymic state [70]. Cognitive impairments are correlated with poor treatment outcome and psychosocial functioning. Therefore experts have suggested that this should be a main treatment target [71, 72].

4.3.4 Treatment

Biological treatments: The main medications for BP are lithium salts and anticonvulsants/mood stabilizing agents as valproate [73]. Lithium is regarded the first drug of choice for prevention of new episodes as it is more preventive than valproate [73]. Second generation antipsychotics have also recently been found to have mood stabilizing properties, preventing relapses of mood episodes [74]. Treatment against mania includes antipsychotics and mood stabilizing agents. Lithium is fairly effective with a number needed to treat (NNT) of 6 [75, 76].
These three kinds of medication target different receptors and pathways, but it has recently been suggested that impact on glutamate may be an important aspect of lithium, anticonvulsants and antipsychotics [77-79].

Antidepressants are commonly used against bipolar depression, although the evidence for effectiveness is sparser than their effect against unipolar depression. They may increase the risk of affective shifts. Thus it has been suggested to limit the use of antidepressants in bipolar depression [80]. In small studies, bipolar depressed patients have been found to have an equal treatment response to Electroconvulsive therapy (ECT) as unipolar depression [81], but there are few studies of ECT treatment.

Psychosocial treatment: Approaches such as psycho-education, cognitive behavior therapy, and family therapy have shown benefits as adjunctive treatments [82]. As in SCH, a long duration of untreated illness is associated with poorer outcome [83].

4.3.5 Pathological mechanisms

Genetic mechanisms: It has been difficult to identify the specific genetic factors conferring the risk of BP. Many genes susceptibility genes are similar to those found for SCH, but genes in the MHC region seem less associated with BP than SCH [24]. In 2008, it was reported that a calcium- related gene called CACNA1c conferred risk genes of BP. This has been replicated in later studies [84]. This gene has also been associated with cardiovascular disease [85]. Another susceptibility gene is important for the function of sodium channels (ANK3), further implicating that genes regulating neuronal excitability have impact on the susceptibility [86]. A gene with previously unknown function, ZNF804a (C2orf10) is a susceptibility gene for both SCH and BP. It has been associated with cognitive function, although studies have found somewhat different

results [87]. The only somatic disease that has described association with this gene is a type of lymphoma [88].

Neuronal processes: According to Post's kindling hypothesis [89], major stress is required to trigger the onset of BP. Stress also increases risk of the first relapses. However, the later relapses seem to occur more and more independent of stressing life events. Episodes may eventually occur autonomously, which could be due to kindling processes in the brain. However, some studies are inconsistent with these findings [2].

Disturbed neurotransmission: No distinct pathology of neuronal function has yet been identified in bipolar disorder. However, since lithium and mood stabilizing drugs have effect on intracellular signal transduction, much research has been done to clarify these mechanisms. It has been found that lithium modifies inositol, and depletion of inositol has been suggested to be a central abnormality of BP [90]. Dysregulation of calcium signaling has also been suggested to be of importance, and calcium signaling has been reported in several studies [84, 91]. Also glutamate signaling has been found disturbed [2]. Magnetic resonance spectroscopy studies have suggested that disturbances in glutamate may be opposite in mania and depression [92]. New research suggests that a disordered circadian system and sleep disturbances contribute to the symptomatology of BP [93].

Neurodevelopment/altered neuroplasticity: Reduced brain volumes, reduced hippocampus, and reduced brain stem volumes have been found in BP [94]. Signs of reduced thalamus, nucleus accumbence and cerebellar cortex have also been presented [94].

Immune related factors: There is no explicit immune hypothesis for BP, but the importance of immune related disturbances in the pathophysiology has been reviewed in recent years [95, 96]. There are fewer studies regarding immune related processes in BP than in SCH, and the main support for immune alterations in BP comes from studies regarding inflammation. (More information about this is presented in section 3.4.4 and 3.6.3).
Two studies have also presented data regarding cognitive function and infection with HSV. They presented similar results as in SCH, i.e. that HSV was associated with poorer abilities on cognitive tests [97, 98]. There are few consistent studies regarding immunomodulating properties

of medication, but lithium and antidepressants have been reported to stimulate immune function and have anti-infective properties [99].

4.4 Similarities between schizophrenia and bipolar disorders

BP and SCH share many similarities and it may be difficult to differentiate the two disorders in the initial phases [100]. The diseases have overlapping risk genes, both patients groups are also vulnerable to stress. Prenatal infections have been found a risk factor of SCH, but is not documented in BP. Both disorders have a peak of onset in early adulthood. The diseases also share symptoms as psychosis, cognitive impairments, depression and elevated risk of suicide. The disease course is often fluctuating with relapses and remissions in symptoms in both diseases. Both disorders may be treated with antipsychotics. Both diseases are also characterized by brain volume reductions in subcortical regions and of ventricular enlargements [94].

4.5 The immune system

The immune system is a wide term describing biological structures and processes that protects against disease and promotes survival [101]. The main tasks of the immune system are to identify and destroy pathogens, tumor cells and traumatized cells. Immunological competence in a host is a result of both genetic constitution and of the immunological experience acquired from previous infections and immunological challenges [102].

4.5.1 Innate and adaptive immunity

The immune responses are divided into innate (natural) and adaptive (acquired). Adaptive responses are stimulated by specific properties of a pathogen which has infected the person. The adaptive response implicates that the immune system keep memory of previous challenges, so that it is able to react more rapid if this pathogen occurs again [103]. Adaptive responses are mainly mediated by lymphocytes, especially T- and B-lymphocytes. Adaptive immune responses include those related to immunoglobulins (antibodies).

It is the innate immune system which has been most investigated when it comes to the interaction between mental disorders and immunology [104]. This part of the immune system will be the focus in this thesis. Innate immune responses are non-specific and exist prior to exposure of specific pathogens. These kinds of responses react to molecules which are commonly found in

pathogens, as well as to common signs of traumas [103]. The innate immunity is mainly made up by mechanical barriers as skin, intestines and the blood- brain barriers, by immunological molecules in the serum and other bodily fluids, and by phagocytic cells as macrophages and neutrophils, which may engulf and eliminate pathogens and traumatized tissue [102].

The complement cascade is also a part of the innate immune system, and involves series of plasma proteins reacting in a cascade. The complement factors bind to pathogens and may induce destruction (lysis). The binding also attracts phagocytes and enhances elimination of pathogens. The innate immunity is also responsible for the immediate responses to traumas, including clot formation to stop bleeding. One mechanism is that complement increases the endothelial secretion of thrombosis promoting molecules [105].

4.5.2 Major Histocompability Complex (MHC)

A genetic region on chromosome six, called the Major Histocompability Complex (MHC), has central immunological functions [102]. Among the most important genes are the Human Leucocyte Antigens (HLA). HLAs are expressed by virtually all cells, and are necessary for the recognition of the body's own cells, in contrast to cells from foreign pathogens. In order to transplant an organ from one person to another, the HLA genes must be very similar, or else the immune system will destroy the new organ. HLA genes are involved in the pathology of many diseases, and have been associated with inflammatory diseases, infections, autoimmune diseases, cancer, cardiovascular disases, brain diseases as well as with SCH [102, 106]. HLA have also been implicated in normal cognitive processes. It has, however, been difficult to find which of the specific genetic variants in the MHC region that are responsible for different diseases. This is due to a large number of exsisting variants, and to that many of the genes in the MHC region are linked and inherited together [107].

4.5.3 Cytokines

Cytokines are polypeptides secreted by cells, with key features of being pleiotropic (the ability to induce different biological responses in different cells)[102]. They are also paracrine (modulate their nearby cells by binding to receptors on their surface), autocrine (modulate the cells that secrete it), synergistic (act in concert with other cytokines to achieve greater effects than the summation of their individual ones), and endocrine (modulate cells and organs in other parts of the body). Cytokines typically first elicit a local effect, but as they spread and come into

circulation, they may affect other organs [102]. The liver cells typically respond to the cytokines by secreting acute phase proteins as C- reactive protein (CRP). The bone marrow typically reacts to the cytokines by increasing the release of neutrophil leukocytes. The fat and muscle cells respond by increasing their energy mobilization [102].

A large number of cytokines have been discovered. As the knowledge about them has increased, they have become markers of different pathological conditions [102]. Tumor necrosis factor alpha (TNF-α), Interleukin 1 beta (IL-1β) and Interleukin 6 (IL-6) are three central cytokines that have been extensively investigated. Although all cells may secrete cytokines, monocytes and macrophages tend to produce more of them than other cells [108].

4.5.4 Inflammation

Inflammation literally meaning "to set on fire", referred originally to the heat, redness, pain and swelling in infected body parts. Inflammation is a part of the innate immune response which serves to bring immune cells to the site of an infection or trauma, where they are needed to phagocyte damaged cells or pathogens and to start the repair process.

The immune cells produce inflammatory signaling molecules including histamines, prostaglandins, leukotrienes and cytokines, to further promote the innate response[103].The complement cascade is also involved inflammation and serves to increases the defense against pathogens [109]. Endothelial cells of the vessels are highly involved in inflammation. They respond to inflammatory signals by expressing adhesion molecules, growth factors and other molecules that promote coagulation of the blood. By this, they restrict bleeding and spread of pathogens [110].

In addition, platelets may contribute to the processes by excreting inflammatory mediators [111, 112]. During inflammatory processes, the inflammatory molecules reach the circulating plasma. This is often referred to as systemic inflammation [113]. Molecules which restrict the inflammatory response are also necessary and are secreted during inflammation. They are called anti-inflammatory mediators. Both inflammatory mediators and anti-inflammatory mediators are often elevated in systemic inflammation. Both types may be assessed as markers of inflammation. Inflammation has been linked to behavior such as exercise, sleep, alcohol abuse, and smoking, as well as with medical conditions including coronary artery disease, obesity and insulin resistance, osteoporosis, pain, autoimmune diseases and cancer [96].

4.5.5 Central inflammatory markers

There is a range of inflammatory molecules. Some of the first discovered and most investigated are described here.

4.5.5.1 Tumor necrosis factor alpha (TNF-α)

TNF-α is a general pleiotropic cytokine, involved with regulation of cellular life or death, and of synaptic integrity and ion homeostasis [114]. It has been described as having two main effects, a antiviral effect and an anti-cellular effect [115]. TNF-α mediates its effects through its two receptors, TNF-R1 and TNF-R2. The TNF-R1 contains a so-called death domain [116] which implies the ability to signal that another cell should die through a process called apoptosis [103, 117]. Apoptosis is an important immunological defense strategy [118] as it enables the killing of infected cells and of cancer cells [38, 46, 49, 116]. In some autoimmune diseases, TNF-α signaling is involved in destructive cell processes. Therefore TNF-α inhibitory medications is effective against autoimmune diseases as rheumatoid arthritis and ulcerative colitis [119].

4.5.5.2 Interleukin 1–beta (IL1-β)

The levels of IL1-β increases rapidly after a bacterial infection[120] and is also important for defense against viruses [121]. It has a major impact on autoimmune diseases. Therefore, antagonists of IL-1β have become widely used as medication for autoimmune diseases as psoriasis and rheumatoid arthritis. Although it is a central pleiotropic cytokine, with some similar effects as TNF, an increase in IL-1β in the brain, tends to downregulate peripheral levels of TNF-α [122].

4.5.5.3 Interleukin 6 (IL-6)

IL- 6 is one of the earliest discovered cytokines, and has been intensively investigated. It increases in response to infections and is regarded a central inflammatory marker [123]. IL-6 is produced by working muscles and increase in response to physical challenges [124]. This increase in IL-6 has anti-inflammatory effects [125] which is in line with other studies reporting anti-inflammatory properties of IL-6 [126].

4.5.5.4 C-reactive protein (CRP)

CRP was the first acute-phase protein described, and it is a well-known systemic marker of inflammation [127]. It increases more in response to a bacterial infection than a viral infection and therefore has become widely used to improve clinical diagnosis of infections [128]. While

virtually all cells may produce of IL-1, IL-6 and TNF-α, only the liver cells produce CRP. CRP binds to the surface of on pathogens promoting phagocytosis, increasing the efficacy of phagocytosis of apoptotic cells [129]. It also activates the compliment system which further promotes phagocytosis [130]. High levels of CRP has been associated with atherosclerosis and cardiovascular disease [131]. IL-6 is a main inducer of CRP while TNF-α has been found to antagonize this stimulatory effect [132].

4.5.6 Other cytokines/inflammatory markers

Interferon were discovered early, and has been much investigated [102]. They were given their name because of their ability to interfere with viral replication, but has later also been found to increase in response to bacterial infections [103]. Interferon is divided into three main groups: interferon-α mainly deriving from leukocytes, interferon-β mainly from fibroblasts and interferon gamma mainly from lymphocytes. Interferon has been used as treatment against multiple sclerosis, hepatitis C and cancer. This immune-modulating treatment may induce psychiatric side effects as irritability, mania, depression and psychotic symptoms [133, 134]. Many other cytokines have been [135] discovered. There are for example more than 35 classes of interleukins [102], and each interleukin may consist of several subtypes.

4.6 The immune system and the brain

Immunological responses may influence virtually every aspect of brain function relevant to mental function [136]. Several aspects of brain functions are influenced by immunological processes, both at the cellular level (synaptic plasticity, neuroendocrine function, neurotransmitter metabolism), and at the functional level (motor activity, fatigue, sleep, appetite, motivation, anxiety, mood and memory) [136]. However, the immune system in the brain is quite different from the rest of the body. The brain is protected from many antibodies by the blood brain barrier (BBB), and the brain is often called immunity-privileged. The immune system also seems to play a separate role in basic neuronal functions which are not per se immune-related [135].

4.6.1 Immune cells in the brain

The brain mainly consists of neurons and glial cells. Ordinary immune cells found in the rest of the body are not usually present in the brain. However, the brain glial cells have immunological properties. The microglial cells are the key innate immune cells of the brain. They survey the environment around the neurons and are specifically adapted to sense various types of danger and differentially react with reparative immune responses [137]. They are able to mediate immune processes between the peripheral immune system and the brain [138]. Astrocytes are the most abundant glia cell in the brain and they have the ability to express MHC class 2 molecules, which are mainly expressed by immune cells. They also express molecules and cytokines which are critical for immune cell activation [139]. The fact that glial cells have many typical immune cell characteristics may lead to high sensitivity to immune related signals, and expression of immune related molecules. A close interaction between brain and immunological processes may be the result.

4.6.2 Immune molecules in neuroplasticity and brain development

The last few years, intriguing links between neuronal processes and immune molecules have been discovered. Several lines of evidence support that immune related molecules and inflammatory mediators are important for basic cognitive processes as learning and memory [135]. This was shown in a study that investigated molecules involved in the process of long-term memory consolidation. They found upregulation of the immune molecules MHC and Complement, while molecules involved in cell death signaling (apoptosis) were down regulated [140]. Several studies have also shown that central cytokines as IL-1β, IL-6 and TNF-α participate at the molecular level in cognitive functions, which has been described as a cytokine model for cognitive function [141]. The model describes how cytokines play intimate roles in the molecular and cellular mechanisms necessary for normal learning and memory processes [141]. Two mechanisms by which TNF-α participates in memory processes, are by altering the expression of MHC molecules [135] and by regulating the strength of neuronal synapses in a process called synaptic scaling [142].

Immune related molecules are also important for normal brain development. In line with this, elevated inflammation during pregnancy induces morphological abnormalities in the offspring. These abnormalities have been found to have similarities to those found in severe mental

disorders [143]. Furthermore, animals lacking cytokines as TNF-α or IL-1β do not develop proper memory function and show signs of neurodegeneration [144, 145].

4.6.3 Blood brain barrier/ immune privilege

The brain is protected from toxic molecules and infectious agents by the BBB, a tight membrane through which large molecules normally cannot pass [146]. Therefore, usually compounds in serum cannot be assumed to have the same concentration in the brain. The immune responses in the brain are also more restricted. This phenomenon is thought to be adaptive as it secures the preservation of neurons. It is generally better that the immune system accepts a low virulent infection than to kill a neuron [147]. The restricted immunological response may be beneficial for pathogens, and is called the immune privilege. Although the BBB protects the brain from peripheral molecules, recent data have shown that peripheral cytokines can cross the intact BBB [147, 148].

4.6.4 Brain /body immune communication

When the brain perceives psychological challenges or psychological stress, it may influence the immune system through signaling through autonomic nerves. These nerves go directly from the brain to the spleen, which is a major immune organ. The brain processes also influence immune processes through nerves to the adrenal glands, which secretes stress hormones as adrenalin, which again has immune suppressive effects [149]. Cortisol is another stress hormone with anti-inflammatory effects [150]. However, the effect of stress on immunological responses is complicated, and may not always be suppressive. Mental stress may also lead to aggravated inflammatory responses [151]. During peripheral infections, the cytokines have been found to mediate several effects in the brain [152]. They typically induce sleepiness, loss of appetite, increased fatigue, more pain, poorer cognition and negative feelings [153].

4.6.5 Inflammation and cognitive impairment

High levels of systemic inflammation have been found to have negative impact on cognitive function in both animal and human studies [154]. In conditions under which the immune system is strongly activated by infection, injury, or other stressful conditions, the brain glia cells change their function and secrete high levels of inflammatory mediators [154]. This secretion disrupts

the balance of immune molecules needed in cognitive processes, and it induces detrimental effects on memory, neural plasticity and neurogenesis [154]. In line with this, high inflammation, as assessed by TNF-α, is present in neurodegenerative diseases such as ischemic stroke, Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and multiple sclerosis [155]. High levels of inflammation are also associated with poorer cognitive function in healthy persons. The largest study so far, including 49.000 healthy men, found that low-grade inflammation was associated with reduced cognitive abilities at the age of 18-20 years [156]. Another study in 447 healthy persons found that low-grade inflammation was associated with disintegration of brain structures seen on brain imaging, as well as with reduced cognitive function [157]. In line with these results, a study of 691 healthy persons, found that those who had high inflammation, had increased risk of cognitive decline into dementia during the next years [158].

4.6.6 Neurotropic pathogens

A pathogen is called neurotropic if it is capable of infecting neurons, and does so preferentially [103]. Common neurotropic pathogens are HSV, Varicella-Zoster, Cytomegalovirus, Epstein-Barr, Mumps, Measles, Influenza, Coxsachie, Echo, Rabies, Encephalitis viruses and Borrelia burgdorferi [159, 160]. Herpes simplex virus 2 (HSV2) is the most common cause of brain infection in fetal life and new-born children, and usually results in selective impairments in cognitive function [161]. After the neonatal period, HSV1 is the most common viral brain infection (encephalitis). Toxoplasma gondii infects approximately 30% of the population, but causes overt clinical symptoms in only a small proportion. During chronic infection, Toxoplasma forms cysts which are located in the brain. The parasite has the ability to manipulate behaviour of infected animals and Toxoplasma has two enzymes which potentially could affect dopamine and serotonin transmission [162].

5 Specific research questions in this thesis

5.1 How is the inflammatory profile in serum of schizophrenia and bipolar disorder patients?

It has been suggested for more than fifteen years that inflammation may play a role in the pathology of SCH, and it has been investigated with inconsistent results. A study from 1995 reported that patients did not have elevated levels of TNF-α, IL-6 or IL-1β [163]. Also in 1999 and 2001 studies reported that there were no evidence of elevated cytokines [164]. However, in summer 2007, when the work this thesis started, 62 studies regarding cytokines and SCH had been published [165]. According to a meta-analysis, which was published in 2008, there was evidence of elevated activity in the IL-1Ra sIL-2R and IL-6 [165]. In SCH, there were fewer studies, and most had investigated bipolar mania [166]. The first study investigating both depressed and manic patients was published in 2006, and had included 8 bipolar depressed patients [166]. According to a review published in 2009, six studies have compared inflammatory markers in serum of BP patients, independent of affective state. Four of these have found low levels and two elevated levels compared to controls [167]. However, these previous studies are small and the number of inflammatory parameters investigated in the same study are limited. For example, the general marker CRP has not been measured together with other inflammatory markers [167]. This makes it difficult to draw conclusions about degree and type of inflammatoy disturbances [167].

High levels of inflammation is associated with cardiovascular disease (CVD). The most investigated inflammatory marker with respect to CVD is CRP [102]. However, also other general inflammatory markers, TNF, IL-6 and IL-1β have been reported to be risk factors of CVD [168, 169]. It is therefore possible that these markers are related to the high cardiovascular comorbidity in patients [167].

Inflammatory pathways are closely interacting with coagulatory pathways, and the endothelial cells are an important interface for the interaction [110, 111]. Von Willebrand factor (vWf) is a typical endothelial related factor related to both coagulation and inflammation[102]. Endothelial cells form structural basis for the BBB, and the endothelial related vWf influences this barrier. In cases of systemic inflammation vWf increases the inflammatory processes within

the brain [170]. vWf has also been associated with increased mortality [171]. These characteristics make vWf an interesting factor when investigating inflammation in severe mental disorders.

Inflammatory markers are also closely related to platelet derived coagulation mediators. CD40L is a platelet related marker which is associated with increased risk of CVD, although investigated in few studies [172, 173]. CD40L has been found elevated in different forms of dementia, which supports that it may be involved in the pathology of neuropsychiatric disorders [174]. Whether levels of CD40L are elevated in severe mental disorders has not been investigated.

Although there is some evidence of high levels of the same inflammatory mediators (TNF, IL-1β and IL-6) in both BP and SCH [108], it is not known whether the elevations are more pronounced in one of the disorders. Infections in early life increase risk of SCH, but are not associated with increased risk of BP. This difference could be hypothesized to be caused by different degree of immune disturbance. However, no previous studies have compared inflammatory markers in SCH with BP, and thus it is not known if there are differences in their inflammatory serum profiles.

To summarize, several lines of evidence suggest immune disturbances to be of importance in the pathology of severe mental disorders and cardiovascular disease. Inflammatory markers have been investigated in small studies, and have suggested elevated levels of some inflammatory markers, although with somewhat inconsistent findings. No previous studies have investigated whether endothelial related or platelet related inflammatory factors are elevated. Furthermore, it is unknown whether there are differences in the inflammatory profile of SCH and bipolar disorder.

5.2 Is Osteoprotegerin elevated in severe mental disorders?

Calcium-related disturbances have been reported in BP and SCH, although the number of studies is limited [175-178]. That calcium may play a central role in the pathology is supported by that lithium interferes with calcium pathways [179]. Calcium has also been associated with genetic vulnerability as variants in the calcium channel CACNA1c is one of the top susceptibility genes [180]. Furthermore, a proteome analysis of SCH brains found that calcium and immune related

molecules were the most disturbed ones [181]. Calcium has been found to have immune stimulatory effect [182], and thus it may be hypothesized that calcium is involved in immune related pathology of severe mental disorders. However, this has not been investigated earlier.

Osteoprotegerin (OPG) is a marker found to reflect calcium-related inflammatory disturbances [183]. The marker acts as a decoy receptor for a genetic transcription factor called Nuclear factor kappa B (NF-κB) [184]. NF-κB has been much investigated and medications targeting NF-κB and OPG have already been developed [185]. NF-κB is encoding central immune regulatory genes. It has also been found to be involved with regulation of excitatory neurotransmission [186]. Mood-stabilizing medication have impact on NF-κB , and thus it could be speculated that this is of importance for their treatment effect [187]. OPG has also been much more investigated in the pathology of somatic diseases, than in psychiatric, and it has been found to be a risk factor of atherosclerosis and CVD [184]. OPG's relation to calcium disturbances, neurotransmission and CVD makes it possible that it is of importance in the pathology of severe mental disorders. As it is a new inflammatory marker not previously measured in severe mental disorders, it was investigated thoroughly in a separate study.

5.3 Are levels of inflammatory markers associated with affective state?

Despite the emergence of a more reproducible pattern of elevated systemic inflammation in BP, the results from different studies are inconsistent [188]. A key feature of BP is the large variation in mood: Periods with high spirits, high energy and reduced need for sleep, then shift to depressed mood reduced energy and increased need for sleep. Symptoms as increased sleep, reduced energy and mood are also commonly seen in conditions with high levels of inflammatory mediators [189]. Therefore, it has been hypothesized that inflammation may be contributing to pathology of depression. In addition, according to a recent review of research, it is evidence of high levels of the inflammatory markers TNF-α and IL-6 in unipolar depression.

However, there is no evidence of high IL-1β or interferon. On the contrary, the mean levels in depressed patients of those markers were non-significantly lower than in controls [190]. Another review recently showed that depression seems characterized by both immune suppression and activation. It has also been speculated whether shifts in inflammation may induce a shift in affective state. A study of healthy volunteers showed that after an immune

challenge with increased levels of inflammation, a normalization of inflammatory markers was associated with elevations in mood [191].

Most previous studies in BP have investigated inflammation in manic state [166]. In 2008, seven studies had measured inflammatory markers in patients with mania. All of them reported that some of the inflammatory markers were elevated [192-200]. Up to 2009, four studies had found elevated levels of inflammation, two had found normal levels [192, 197-201], and one study had found that some markers had an inverse pattern in manic versus depressive state [200]. As the studies in bipolar depression are inconsistent, and are heterogeneous in sample compositions, cytokine assessments, treatment regimens and ethnic groups, it was difficult to compare results from the different studies [96]. It was a lack of studies comparing levels of inflammation in mania, depression, and neutral affective state, with inflammation in healthy volunteers would help interpret results [96]. A study investigating if inflammation is associated with severity of mood symptoms, would also be of importance, as no studies so far has reported any significant associations [96].

Inflammation has been associated with mood symptoms in different diagnostic categories as unipolar depression and mania. BP share some similarities with SCH, Mood symptoms are prevalent in both disorders [2, 6, 202]. However, how inflammation relates to mood symptoms in SCH patients is not known. It could be hypothesized that mood symptoms will be associated with inflammation in a similar way across diagnostic boundaries. However, it is also possible that inflammatory mediators are involved in the core pathology of affective dysregulation of BPs, while not involved in mood symptoms in SCH. This has, however, not been investigated in any study.

6 Aims

The overall aim was to gain more knowledge about the role of inflammation in severe mental disorders.

The sub aims were:

1- To determine if patients with severe mental disorder have elevated inflammation compared to healthy controls, and to identify any specific inflammatory pathways that may be disturbed.

2- To evaluate if the inflammatory profile was different in patients with BP compared to those with SCH.

3- To determine if levels of OPG were different in patients with SCH and BP compared to healthy controls, and in SCH compared to BP.

4- To examine if inflammatory markers were associated with affective state.

7 Methods

7.1 Subjects

Patients: The study was carried out in the catchment area of the University Hospitals of Oslo, Norway, including patients from both inpatient and outpatient treatment units. The patients were included through referrals by clinicians working in the treatment units. The inclusion criteria were known in the psychiatric services of the participating hospitals. The age of the patients was between 18 and 65 years. They had DSM-IV criteria for SCH or BP spectrum disorders, and were willing and able to give written, informed consent of participation. Exclusion criteria were history of moderate or severe head injury, neurological disorder and mental retardation (IQ less than 70).

In the first study patients with autoimmune disorders, use of non-steroid anti-inflammatory drugs or statins were excluded. In the second and third studies, patients with autoimmune diseases were included, increasing the representativeness of the sample. In these studies, results were controlled for differences in autoimmune diseases. In the second and third studies, only those who had both adequate blood measurement of both inflammatory markers and

confounding factors were included. In the first study, there were 311 patients. In the second study, the number was 312. In the third study, 36 fewer patients participated.

Of the 312 patients, 186 (185 in study 1) had a DSM-IV schizophrenia spectrum disorder: (Schizophrenia [n=143], Schizophreniform [n=11] and Schizoaffective disorder [n=33]). 125 had a bipolar spectrum disorder (Bipolar I disorder [n=73], Bipolar II disorder [n=44] and Bipolar not otherwise specified [n=8]). In the third study, there were 22 fewer SCH patients and 14 fewer BP patients due to more strict inclusion criteria regarding affective symptom measures. One more SCH patient was included due to access to new clinical data. The samples in the third study were compared with the samples in study one. The inflammatory marker levels and the clinical and sociodemographic characteristics were not significantly different.

7.2 Controls

A representative control group of 244 healthy volunteers was randomly selected from statistical records in the same catchment area as the patient groups. They were contacted by letter inviting them to participate. Included were controls without a history of medical problems, severe psychiatric disorders including alcohol or illicit substance abuse/dependency, or severe mental disorder in close relatives. In study number two and three, there were five fewer controls, as only participants who had both successful measurements of inflammatory and confounding factors were included.

7.3 Selection of inflammatory markers

It was focused on four central and general inflammatory pathways which previous smaller studies have suggested to be involved in severe mental disorders. In addition to these central markers, three new markers of distinct inflammatory pathways were examined, to find out whether patients had any specific inflammatory disturbances. High frequency of cardiovascular disease is seen in severe mental disorders, and inflammatory markers involved in pathology of cardiovascular diseases were therefore also selected.

Tumor necrosis factor receptor type 1 (TNF-R1): TNF-α is a general inflammatory marker which has been found elevated in previous studies. However, it has a short half-life and low reliability in serum-measurements [203]. TNF's effect is based on binding to its two receptors, TNF-R1 or TNF-R2 [204]. High serum levels of TNF-α induce an elevation of these two receptors. Usually the levels of TNF-α and TNF- receptors are highly correlated [205, 206]. Furthermore, the TNF-α receptors stabilize TNF-α's structure and preserve its activity [207]. Therefore the receptors are reliable indicators of TNF-α activity [207]. TNF-R1 is the major TNF-α receptor in serum [208]. It is stable in serum measurements and has higher accuracy with regard to the follow-up and prognosis of various diseases than TNF-α [209, 210]. Also in SCH, a previous study found elevated levels of sTNFR1, but no difference in TNF-α [211]. Therefore we chose to measure TNF-R1.

Interleukin 1 receptor antagonist (IL-1Ra): IL-1β is a general inflammatory marker, but this marker often circulate in a concentration below detection limit [212]. IL-β exerts its effect through different receptors, and the receptors increase in cases of inflammation [213, 214]. This means that although IL-Ra has antagonizing effects on IL-1β when given as treatment, the IL-1Ra is increased in serum of patients with high IL-1β. IL-1Ra is a receptor for IL-1β which has been found to have reliable properties in serum measurements [209]. Furthermore, IL-1Ra has been found elevated in previous studies of mental illness [165] and therefore we chose to measure this marker.

Interleukin 6 (IL-6): IL-6 is a central inflammatory marker, and this marker has been suggested to be included in all further studies of cytokine induced sickness behaviour [215]. Therefore this marker was included.

C-reactive protein (CRP): This is the prototypical inflammatory marker widely used in diagnosis of bacterial infections [128]. Contrary to the three previous general markers, it is produced in the liver. High sensitive CRP (hsCRP) is the inflammatory marker which has been most investigated as a marker of cardiovascular risk [131], and therefore this marker was included.

Von Willebrand factor (vWf): Von Willebrand factor (vWf) is an endothelial related inflammatory marker [216], important for proper hemostasis and coagulation [217]. vWf influences the blood brain barrier and induces brain inflammation in models of encephalomyelitis [170]. A lack of vWf results in bleeding disorders [218], while high levels is associated with thrombosis [219]. VWf has not been measured in severe mental disorders, and therefore we selected this marker.

CD40 ligand (sCD40L): The soluble form of CD40L (sCD40L) is derived mainly from activated platelets [220], which makes this a good marker of platelet related inflammation. CD40L is associated with cardiovascular diseases [221], with dementia and with marked depression [222-224]. Levels of sCD40L have never been measured in severe mental disorders, and therefore this marker was selected.

Osteoprotegerin (OPG): As described in section 3.6.2, OPG is a novel inflammatory marker reflecting activity in the central inflammatory transcription factor NF-κB. OPG circulates at much higher levels than the receptor activator of NF-κB (RANK) it has been found to be a stable measure of RANK/RANK ligand activity [184]. As it is a new marker and calcium related genes are susceptibility genes for severe mental disorders, OPG was investigated more thoroughly in a separate study.

7.4 Design

The study was organized through the multicenter study called "Tematisk Område Psykose" (Thematically Organized Psychosis (TOP) Study). TOP was initiated at Oslo University Hospital, Ullevaal, in 2002. Later, the catchment area of the study has been extended, and researchers from several other hospitals in Norway have joined the study group. The TOP study is approved by the Regional Committee for Medical Research Ethics (2009/2485) and by the Norwegian Data Inspectorate(2003/2052). The biobank is approved by the Norwegian Directorate of Health (200403453). The catchment area includes Oslo and surrounding areas. It includes approximately one million inhabitants. The current study is naturalistic, cross sectional involving group comparisons.

7.5 Clinical Assessments

The assessments were conducted by psychologists or MDs, with specific clinical psychiatric training. The assessments generally took place over two sessions including a diagnostic interview, assessment of symptoms, a physical examination and a blood withdrawal. Patients had a physical examination at the day of the blood sampling and were free of infections, supported by hsCRP below 20 ng/ml, and were stable, not in an acute phase.

7.5.1 Diagnostic interview and clinical characteristics

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes. Inter-rater reliability was good, with an overall kappa score of 0.77 (95% C.I: 0.60-0.94) for diagnoses. Global assessment of symptom severity and functioning was measured with the Global assessment of functioning (GAF) Scale (split version). The intra class correlation coefficient, one-way random single measures (ICC 1.1), were 0.86 for both symptom and function GAF scores. The Structured Positive and Negative Syndrome Scale (SCI-PANSS) was also used, and total scores were recorded to indicate general symptom severity [225]. Information about age, gender and ethnicity were recorded. Ongoing medication with mood stabilizers, lithium, antipsychotics or antidepressants and of somatic medication was also noted. Smoking habits, the intake of alcohol (number of alcohol units) and the use of illegal substances (number of times) the last two weeks was registered. Furthermore, medical history was noted, especially if they had diagnosis of diabetes, cardiovascular or autoimmune disease, as well as height and weight for body mass index calculation.

7.5.2 Mood assessment

The severity of manic symptoms was measured with Young Mania Rating Scale (YMRS) [226] and depression with Inventory of Depressive Symptomatology (IDS) [227], and a SCH subgroup was only evaluated with Calgary Depression Scale for Schizophrenia (CDSS) [228].

In study III, three affective state groups were defined. The groups were based on validated cut off scores for mania on the YMRS, and on validated cut off scores for depression on IDS, together with an evaluation of the core symptoms of mania and depression.

“Neutral” mood group was defined as total score on YMRS < 8, and the core item elevated mood = 0. In addition, total score on IDS < 14 and core item sad mood = 0.

"Elevated" mood group was defined as total score on YMRS > 7 or the core item elevated mood ≥ 1. "Depressed" group was defined as total score on IDS > 14 or core item sad mood ≥one.
In 37 SCH patients and 4 BP patients the depressive symptoms had only evaluated with CDSS [228]. This scale has similar to IDS a core item for sad mood, "depressed mood" that consists of 4 levels, and the total CDSS cut-off score for depression is 7 [229].
In patients evaluated with CDSS "Neutral" was defined as a score of 0 on core item "depressed mood " together with a total score on CDSS <7, and "Depressed" was defined as core item sad mood ≥ 1 or CDSS total score ≥7. Patients who had a score ≥1 on both core item elevated mood on YMRS as well as core item sad on IDS/CDSS or had missing for one of the scales were classified as "Mixed group". This group consisted of 11 BP and four SCH patients and was not included in the analysis of affective states, only in the correlation analysis of affective symptom levels.

7.6 Laboratory analyses

The blood was drawn between 8am and 5pm, and the time for the blood sampling was recorded. The time difference between blood sampling and clinical assessment was also recorded.

Plasma levels of sTNF-RI, IL-1Ra, CD40L, IL-6 and OPG were measured by enzyme immunoassays (EIA) obtained from R&D Systems (Minneapolis, MN, USA). Plasma concentrations of vWf were measured by EIAs using antibodies from DakoCytomation (Norway) as described by Bollerslev [230]. Levels are given in plasma concentration percent (%). The standard curve is based on samples from a plasma pool of healthy individuals, were the normal range is arbitrary set to 70-130%. All intra- and inter-assay coefficients of variance were <11%.

Blood samples were analyzed regarding kidney function (creatinine), liver function (alanine aminotransferase; ALAT) and dyslipidemia (cholesterol and triglycerides) and glucose levels. These clinical blood sample analyses (hsCRP, creatinine, alanine aminotransferase; ALAT, cholesterol, triglycerides, glucose) were performed according to standard procedures at Department of Clinical Chemistry, Oslo University Hospital, Oslo, Norway.

8 Statistics

8.1 Statistical tests

All Statistical analyses were done using the SPSS Software package for Windows, version 15.0 (SPSS, Chicago, IL, USA). All tests are two-sided with a preset level of significance of 0.05.

Four markers (IL-1Ra, hsCRP and IL-6 and CD40) were significantly skewed. In the first study these markers, as well as TNF-R1 and vWf were analyzed with nonparametric tests. Spearman's Rho was used for correlation analysis and Kruskal–Wallis test for comparisons with three groups. Mann–Whitney U-test was used for post-hoc analyses. The latter was corrected for multiple testing through Bonferroni correction.
OPG values were normally distributed and students T-tests were used to compare the patient group with the controls. To test if the variance differed between the groups, Levene test for equality of variances was used. Differences in the level of OPG across the two diagnostic groups together with the controls were analyzed by use of a 1-way analysis of variance (ANOVA) with a Tamhane's post-hoc correction.

In study III, markers that were not normally distributed were logarithmically transformed in order to obtain normal distribution. It was first analyzed if there were different levels of immune factors in different affective state groups, by doing ANOVA with a three level model (depressed = 0, neutral = 1, and elevated =2). As post-hoc test Tamhane's test was used, which is a test based on unequal variances in the groups. Students T-tests were used to compare affective groups with controls. It was also analyzed if there were group differences with ANOVA, giving the same results (analysis not presented in the study)
To investigate if levels of immune factors were correlated with severity of depression or mania, Pearson's correlations test was used. These analyses were done separately for BP and SCH.
To find out how much of the variance in one inflammatory marker that was explained by the other markers, linear regression was used. The marker was put as dependent into a linear regression analysis, with all the other markers as independent variables. The R square for the total model was calculated to find how much of the variance that was explained by the other

markers.

8.2 Analysis of correlations between the inflammatory markers

Cytokines share many properties and have diverse effects. It was possible that the different inflammatory markers were highly correlated. If so, it would be uncertain if the markers represented specific inflammatory pathways. Therefore, correlation analysis between the markers was done.

In the first study, correlation analysis between the inflammatory markers, measured with the non-parametric Spearman's Rho test was done. In the total sample, STNF-R1 was the only marker that correlated significantly with all other markers, with highest r-value for vWf (r= 0.28) and the lowest for hsCRP(r=0.2) ($p < 0.00001$). In addition to TNF-R1, VWF correlated only with IL-1Ra ($r = 0.15$, $p < 0.0005$). The strongest correlation was seen between IL-6 and hs-CRP ($r = 0.48$, $p < 0.00001$).

Smoking habits among the patients did not significantly correlate with sTNF-RI, vWf, or hs-CRP. The inflammatory cytokines were not correlated to the cortisol levels in patients, except for hs-CRP, which had a small positive Pearson correlation coefficient with cortisol of 0.12 ($p = 0.04$).

In study III, in the total sample of patients and controls, Pierson's correlations were used to test correlations between inflammatory markers. The analysis showed that sTNF-R1 and Log transformed IL-1Ra had the strongest correlation (n=503, r= 0.40, p<0.001), OPG and IL-6 had the weakest (n=503, r=0.10, p=0.02) while IL-1Ra and hsCRP were not significantly correlated (n=498, r=0.06, p=0.17). The combined effect of other inflammatory markers explained 25 % of the variance in sTNF-R1, 11 % of the variance in vWf, and 8% of the variance in OPG, 15% of IL-6, 14% of hsCRP and 14% of CD40L.

In study III, there were significant correlations between the mood measures. Total score on IDS in BP patients was highly correlated with sad mood (n= 222, r=0.78, p<0.001) while total score on YMRS was moderately correlated with elevated mood (n=265, r=0.39, p<0.001). Total YMRS was only moderately negatively correlated with total IDS score (n=222, r=-0.24, p<0.001). When two inflammatory markers were correlated with the same mood symptom measure, a regression

analysis was done to investigate if the markers were independently correlated with degree of mood symptoms.

8.3 Control for possible confounding factors:

8.3.1 Confounders, study I and II

To control for differences in factors which could have been differently distributed between patients and controls, hierarchical multiple linear regression analyses were used. The possible confounding factors were added as independent variables into a regression analysis for predicting levels of the inflammatory markers. The BP and SCH patients were gathered in one group, and a variable of patients versus controls was entered into the linear regression as the last step.
In study II, the linear regression did not include cortisol levels or time at blood sampling due to lack of complete information in all subjects.

8.3.2 Confounders, study III

The study investigated differences in smaller groups of patients, and wanted to control for many possible confounding factors. It is recommended to have ten times higher number of cases than independent factors in a linear regression sample, and not all independents could be included into the same regression analysis. An evaluation of which factors that most likely could confound the results was done.
A factor may confound an association between inflammation and affective groups only if it is correlated with an inflammatory marker and is differently distributed between the groups. Therefore, it was first analyzed if there were any differences in the distribution of possible confounding factors between the three affective groups or between affective groups and controls by performing ANOVA. All differently distributed factors and factors that were bivareately correlated with immune markers were than analyzed together with ANCOVA to see if they had a combined effect on immune markers.

To control confounding factors in the correlation between immune markers and mood symptoms a bivariate correlation analysis investigated associations between the confounding factors, immune markers and mood symptoms. The combined effect of all possible confounders that were significantly correlated with either mood symptoms or immune markers was controlled with a

linear regression analysis. In addition, models including factors which were not correlated with either mood symptom or the immune markers were put into the regression model, without having any significant impact.

9 Results

9.1 Study I

9.1.1 Are inflammatory markers elevated in severe mental disorder?

The combined patient group had highly, statistically significantly elevated levels of two inflammatory markers: sTNF-RI and vWf compared to the healthy control group, ($p<0.000002$ for both) (Table 2). The increase was 17 % for sTNF-RI and 27 % for vWf (Table 2, Study I). In contrast, there was no significant difference in the levels of IL-6, sCD40L or IL-1Ra between the patients and the controls, but hs-CRP was significantly elevated ($p=0.02$). Also in unmedicated patients there was a significant increase in plasma levels of sTNF-R1 (1.09 versus 0.91 ng/ml, $p<0.001$) and vWf (101 versus 77 %, $p<0.007$) as compared with concentrations in healthy controls.

These elevations remained significant also after controlling for possible confounders. There were no significant differences in any inflammatory parameters between medicated and unmedicated patients.

Limiting the analysis to patients with strict SCH and BP I (i.e. excluding patients with Schizoaffective, Schizophreniform, Bipolar disorder II, and Bipolar disorder not otherwise specified), the immune profile was still similar and the elevations remained statistically significant (data not shown).

As seen in table 2 of study I, there was a trend that SCH patients had higher levels of IL-1β than controls, but the difference was not significant. However, since there are indications of diurnal variation in inflammatory markers [231], it was analyzed whether there were correlations between timing of blood sampling and inflammatory markers. None of the markers were

correlated with timing except from IL-1Ra (r=0.13 - 0.14, p=0.03 – 0.06). Therefore, the levels of IL-1Ra in patients and in strictly time-matched controls were compared. It was found that patients had higher levels than these time matched controls (p= 0.007). However, when this result was controlled for possible confounders, the difference was not significant (p=0.17).

9.1.2 Do schizophrenia and bipolar disorder have similar immune profile?

There were no significant differences in levels of any inflammation markers between the two diagnostic groups. When each diagnostic group were compared to controls, they both showed highly significant elevations of sTNF-RI ($p < 0.001$) and vWf ($P < 0.005$) (Table 2, Study I). A difference in hs-CRP levels did not remain significant when the patient group was divided into SCH and BP, probably due to loss of statistical power.

9.2 Study II

9.2.1 Do patients have elevated levels of osteoprotegerin?

OPG levels in patients and controls are shown in table 2, study II. The mean OPG level was 10% higher in the patient group (Mean±SD; 2.78 ±1.47 ng/ml) than in the controls (2.52 ±0.92 ng/ml; t=2.6, DF=531, p= 0.01). The comparison of OPG levels across the groups (SCH, BPs, and healthy controls) indicated a significant between-group difference (F=3.1; def. =550; p=0.046) (Table 2, study II). None of these group differences, however, reached the level of statistical significance after corrections for multiple testing (BP vs. controls: p=0.08, SCH vs. controls: p=0.20 and SCH vs. BP: p=0.94).

A regression analyses showed that OPG levels were significantly elevated in the patient group as a whole compared to the controls also after controlling for 11 different factors that possibly could have confounded the result (t=-1.97, d.f.=485, p=0.049) (Table 3, Study II). There were slightly more women among the controls (56%) than the patients (50%). Women also had higher OPG (2.84±1.35) than men (2.48±1.14) (p=0.001), but in the overall sample the group x gender interaction term was not significant (p = 0.35).

There were some differences between the diagnostic subgroups, were schizoaffective disorder and bipolar disorder type II had the highest levels. However, the differences did not reach

statistical significance: SCH (n=143) 2.72±1.36; Schizophreniform (n=11) 2.25± 0.67; Schizoaffective disorder (n=33) 3.04± 2.13; Bipolar I disorder (n=72) 2.76±0.05; Bipolar NOS (n=8) 2.22 ±0.34; Bipolar II disorder (n=45) 3.06±0.92. Within the patient group as a whole, OPG was positively correlated with age ($r=0.15$, $p<0.001$) and female gender ($r=0.15$, $p<0.001$).

OPG was positively correlated with cholesterol and hsCRP (cholesterol: $r=0.14$; hsCRP: $r=0.17$, $p<0.001$). OPG was weakly negatively correlated to creatinine ($r=-0.09$, $p=0.04$). There were no significant correlations between OPG levels and BMI ($r= 0.03$, $p= 0.6$). OPG levels in 239 non-obese subjects (BMI < 30) had BMI of mean ±SD 24.1 ± 3.26 kg/m^2 were also significantly higher compared with controls (2.79 ± 1.5; versus 2.52 ± 0.92; $t=2.3$, d.f. =391, $p = 0.021$). OPG was still significantly elevated in patients versus controls also after control for glucose and cholesterol, which are traditional risk factors of metabolic syndrome.

Patients not treated with antipsychotics (n=80) had significantly higher OPG than controls (mean ±SD 2.93±1.41 ng/ml vs. 2.52±0.92 ng/ml; $t=2.4$, d.f. =102, $p=0.02$). In addition, there was no difference in mean OPG between the patients using first and second generation antipsychotics (first generation antipsychotic: n=19 [OPG 2.64±0.89 ng/ml] and second-generation antipsychotics; n=242 [OPG 2.78±1.50 ng/ml; $t=-0.44$, d.f. = 259, $p=0.6$]). The analyses suggest that medication did not confound the results.

9.3 Study III

9.3.1 Are markers of inflammation associated with different affective states?

As seen in Table 2, study III, the levels of all inflammatory markers were lowest in the depressed group of BP. All markers were higher in the Elevated mood group than in the Depressed group. Neutral mood group had intermediate levels of four markers, and highest levels of markers IL-6 and hsCRP. There were significant differences across affective groups. sTNF-R1 and IL-1Ra differed significantly in Depressed vs. Elevated ($p= 0.007$ and $p=0.04$ respectively), OPG and IL-6 differed significantly in Depressed vs. Neutral,($p=0.04$ and $p=0.01$ respectively).

There were no significant differences in vWf or hsCRP across affective state groups. There was a tendency of increasing levels of inflammatory markers with increasing affective state groups that was significant with respect to sTNF-R1 ($r=0.29$, $p=0.003$), OPG ($r=0.29$, $p=0.003$), IL-1Ra

(r=0.28, p=0.005) and IL-6 (r=0.21, p=0.04). In SCH there were no significant differences across affective state groups and no trend of higher levels in Elevated state group (see Table 2, study III.

9.3.1.1 Inflammation in controls vs. different affective states

Bipolar disorder patients in Elevated mood group had significantly higher levels than controls of four markers, and the difference was significant for sTNF-R1 and vWf (p=0.000005 and p= 0.002 respectively). Patients in Neutral mood group had higher levels of all markers compared to controls, and the difference was significant with respect to OPG and IL-6 (p=0.0003 and p=0.005 respectively). BP patients in Depressed mood group had approximately equal levels as controls, i.e. non-significantly higher levels of TNF-R1, vWf and hsCRP and non-significantly lower levels of OPG, IL-1Ra and IL-6.

SCH patients in Depressed mood group, had higher levels than controls of TNF-R1 and vWf (p=0.0001 and p=0.008 respectively). Patients in Neutral mood group had higher levels than controls of vWf (p=0.02) and patients in Elevated mood group had higher levels of hsCRP than controls (p=0.03).

9.3.1.2 Severity of affective symptoms in relation to levels of inflammatory markers:

The severity of depressive symptoms as measured as total IDS score was significantly negatively correlated to three cytokines: OPG (n=107, r= -0.27, p=0.005), IL-1Ra (n=107, r=-0.30, p=0.002) and IL-6 (n=107 r=-0.27, p=0.006). Severity of the core depressive symptom "sad mood" was also significantly and inversely correlated with these cytokines: OPG (n=111, r=-0.34, p=0.0003), IL-1Ra (n=111. r=-0.31, p=0.001) and IL-6 (n=111 r=-0.35, p=0.0002). Regression analysis showed that OPG and IL-1Ra were independently correlated with total IDS, and that OPG and IL-6 were independently correlated with depressed mood. The other three immune markers also had a trend of negative correlations with depressive symptoms, but this was not significant. The immune markers tended to be positively correlated with the core mania item "elevated mood", which was significant with respect to sTNF-R1 (n=111, r=0.22, p=0.02). Severity of manic symptoms as measured with the total YMRS score was not significantly correlated to markers of inflammation.

In SCH, neither YMRS, IDS nor core affective symptoms were significantly correlated with any immune parameters (Table 3, Study III).

Affective state groups: The trend of higher immune markers with higher affect was significant after control for confounders for sTNF-R1 (p=0.02), OPG (p=0.04), IL-1Ra (p=0.02), while IL-6 lost significance (p=0.09). After control for the combined effect of possible confounders the Depressed mood group of BP still had lower levels than Elevated mood group of TNF-R1 and of IL-1Ra (p=0.04 and p=0.02 respectively). The Depressed group also had significantly lower levels than Neutral mood group of OPG and IL-6 after control for confounding factors (p=0.004, and p=0.005 respectively).

Comparisons with controls: After control for the combined effect of possible confounding factors the BP patients in the Neutral mood group still had significantly higher levels than controls of OPG (p=0.002) and IL-6 (, p=0.007) and patients in the Elevated mood group had higher levels of sTNF-R1 (p=0.009) and vWf (p=0.02). After control for the combined effect of possible confounding the SCH patients in Depressed mood group still had higher levels than controls of sTNF-R1 (p=0.005 but not of vWf (p=0.17), patients in Neutral mood group did not have higher vWf (p=0.17), and Elevated mood group did not have higher hsCRP (p=0.19) than controls.

Affective symptoms: After control for confounders STNF-R1 was not significantly correlated with Elevated mood (p=0.20). After control for possible confounding factors the total IDS score was still significantly negatively correlated with OPG (p=0.02), IL-6 (p=0.02) and IL-1Ra (p=0.01), and the core item sad mood was still significantly negatively correlated with OPG (p=0.007), IL-1Ra (p=0.009) and IL-6 (p= 0.005).

9.4 Summary of results

9.4.1 Patients had a specific immune profile

The patients with severe mental disorder had a specific immune profile of highly significantly elevated TNF-R1, vWf and OPG, making it possible to suggest that these inflammatory pathways are more central to the pathology than other pathways.

9.4.2 Bipolar disorder and Schizophrenia had similar immune profile

Patients had highly significant elevations of inflammatory markers. Of the four general inflammatory markers, sTNF-R1 was highly significantly elevated ($p<2x10^{-6}$), hsCRP was

elevated (p=0.008) but the association lost significance when divided into separate groups, IL-1β was elevated when compared strictly to time matched controls (p=0.007), but the association lost significance after control for possible confounding factors. IL-6 was not elevated. Of the three markers of more specific inflammatory markers, vWf was highly significantly elevated ($p<2x10^{-6}$), OPG was slightly elevated but the association was significant also after control for many possible confounders including CRP (p=0.01) while CD40L was not elevated.
SCH and BPs had the same inflammatory profile, without any significant differences.

9.4.3 Inflammation was inversely associated with degree of depression in bipolar disorder.
Mania patients had the highest levels of inflammation, while depressed BP patients had low levels of all six inflammatory markers. Neutral mood had intermediate levels, and higher than controls. The severity of depressive symptoms was highly negatively correlated with OPG, IL-1Ra and IL-6. Depressed BP patients had different immune profile from manic patients.

10 Discussion

10.1 High levels of inflammation in schizophrenia and bipolar disorder

The investigations of this theses found that patients with severe mental disorders have elevated levels of general inflammatory marker (TNF-R1). The elevations of the general markers were highly statistically significant, were present in unmedicated as well as medicated patients and control for confounding factors did not change the results. In addition, the general marker hsCRP was slightly elevated. There was also some evidence of high IL-1Ra in patients, although it could not be excluded that this was due to confounding factors.

The results are supported by other studies of immune related disturbances in severe mental disorders [108]. The study replicates findings of high inflammation reported in previous smaller studies. According to the most recent review regarding inflammation in severe mental disorders from 2010, there are evidence of elevated TNF-α, IL-1β and IL-6 in SCH, and of the same markers in BPs, although less evidence of elevated IL-6 [108]. The review did not include analysis of CRP and sTNF-RI, which has been found elevated in four recent studies [108, 211,

232-234]. The number of patients in the meta-analysis was approximately 450, which means that the 312 patients in the current study and the patients in the four other recent studies nearly doubles the number of cases, and strongly support that patients with severe mental disorders have elevated levels of general inflammatory markers [235].

The endothelial related inflammatory factor vWf was highly significantly elevated. Measures of this specific inflammatory marker have not been reported in severe mental disorder before. However, a previous study of psychotic disorders has reported association and genetic linkage between bipolar I disorder and the vWf gene [236]. Furthermore, in a study of depression in patients with cardiovascular disease, the vWf gene was the only gene out of 87 genes investigated, that was associated with depression [237]. In addition, in a study in healthy men, vWf was found to be associated with feelings of exhaustion and negative affect [238]. Four studies in severe mental disorders have investigated markers of endothelium function (ICAM and endothelin) in severe mental disorders, and two of them found elevated levels, and two found reduced [108]. These studies suggest that vWf is associated with mental symptoms, and support the current findings of increased vWf in severe mental illness.

The calcium related marker OPG was also significantly elevated after control for confounding factors. The levels of the specific inflammation marker OPG has not been reported before in severe mental disorders, but two small studies have investigated OPG levels in depressive patients. OPG was increased in patients with depressive disorder [239], and decreased in patients with depression and a former history of anorexia [240]. OPG is related to calcium regulation, and the current result is in line with new research indicating that calcium signaling is of central importance in severe mental disorders [241].

Contrary to the current findings, several studies have found elevated serum levels of IL-1β or IL-1Ra in severe mental disorders although, there has been some inconsistencies [108]. IL-1β has, for instance been found both elevated and decreased in the cerebrospinal fluid of SCH patients [163, 242].

Animal studies have suggested a role for IL-1Ra in behavior influenced by social isolation [243], and IL-1Ra increases after psychosocial stress [244]. Social withdrawal is one of the key features of negative psychotic symptoms, which has been associated with IL-1Ra in patients [245].

Preliminary analysis of how IL-1Ra is related to psychotic symptoms, the current sample suggests that IL-1Ra is higher in patients with negative psychotic symptoms [246]. Thus, one could speculate if studies may find different levels of IL-1Ra depending on severity of negative symptoms.

According to a meta-analysis, IL-6 is one of the general inflammatory markers which most studies have found elevated, especially in SCH [188]. The current results are, however, in agreement with recent findings of no increase of IL-6 in SCH [247], and lower IL-6 in the cerebrospinal fluid of BP patients than in healthy volunteers [248].

CD40L has not been measured in previous studies of severe mental disorder. As the mean levels were non-significantly lower in patients than in controls, and as the marker did not have a large variation, it is unlikely that platelet related inflammatory pathways are of central importance to SCH or BP pathology.

10.2 Specific immune profile of high TNF-R1, OPG and vWf

The present results indicate a pattern of increased immune marker TNF, vWf and OPG. They were highly significantly elevated, also after controlling for confounding factors, while the four other markers were not.

TNF-α has been much investigated, There are several indications that patients have an immune profile characterized by high TNF-R1. According to a recent review, 10 immune markers have been investigated in two or more studies of severe mental disorders [108].Two of these immune markers were mainly of endothelial origin, four were mainly of monocytes/macrophage origin, and four were mainly of T-cell origin [108]. The analysis found evidence of elevated levels of the inflammatory markers from monocyte/macrophages, as TNF-α, IL-β, and IL-6, while inflammatory markers of other origins had been found consistently elevated. The meta-analysis found that ten studies had reported elevated levels of TNF-α, seven had reported not significantly different levels, while no studies had reported reduced levels [108]. The meta-analysis, together with the current findings, strongly indicates that the inflammatory profile in patients with severe mental disorders is characterized by high activity in the TNF-pathways, as indicated by TNF-R1.

VWf was also highly significantly elevated after control for confounding factors. vWf is a not general inflammatory marker, but is a marker of endothelial activation and coagulation [249]. Four studies in severe mental disorders have investigated markers of endothelium function (ICAM and endothelin) in severe mental disorders, Two of them found elevated levels, and two found reduced [108]. In addition to vWf, OPG could also be described as related to endothelial dysfunction. OPG is constitutively secreted by endothelial cells [250, 251] and increases the adhesion of immune cells to the endothelium in the vessel walls [251]. Thus, the combined findings of elevated vWf and OPG indicate that patients have endothelial related inflammatory disturbances. New research supports that patients have endothelial dysfunction [252]. While earlier studies which investigated blood pressure and pulse wave variability did not find any clear disturbances [252], a new study found evidence of endothelial related dysfunction. Other aspects of vascular function, however, did not show any major disturbances [252]. This result is supported by a new study showing that the brain capillaries in SCH patients have structural abnormalities [253]. In addition, the susceptibility gene NOTCH4 elicits endothelial cell activation [254, 255]. That high levels of inflammation is related to endothelial inflammation is supported by that inflammatory genes were found to be altered in the brain endothelium of SCH patients [256]. Thus, it is reason to conclude that the patients' immune profile is characterized by endothelial related inflammation.

The inflammatory profile was also characterized by increased OPG, which indicates calcium related inflammatory disturbance. Osteoprotegerin is closely involved in calcium metabolism [176, 257]. Also vWf is influenced by calcium, as vWf has a calcium binding site which regulates its cleavage [258]. Furthermore, calcium is important for the release of TNFR1 from endothelial cells [259]. The inflammatory profile of high OPG, vWf and sTNF-R1 could therefore be characterized as calcium related. The importance of calcium in the pathological mechanisms of severe mental disorders has been proposed in a calcium hypothesis, based on evidence that calcium may be an underlying disturbance causing disrupted dopamine and glutamate transmission [260]. That high inflammation is related to calcium disturbance is also supported by two studies reporting disturbed calcium in immune cells of patients [176, 257].

To conclude, the results in the current thesis suggest a specific immune marker profile characterized by high levels of TNFR1, OPG and vWf, and more normal levels of hsCRP, IL-1β,

CD40L, and IL-6. This profile suggests TNF related, calcium related and endothelial related inflammatory disturbance.

10.3 Similarities between schizophrenia and bipolar disorder

The present study found that inflammatory pathways are activated in BP to the same extent as in SCH. This is in line with recent genetic studies, which have found that most susceptibility genes represent risk of both disorders [24]. Both disorders also have the same disturbance in stress hormone metabolism [261]. The disorders also share main morphological changes, as enlarged ventricles and reduced hippocampus [94].The same type of symptoms has also been found predictive of functioning irrespective of diagnosis [262].

The associations of immune markers and mood characteristics were only observed in BP. Even though the current BP sample showed less variation in mood, especially lower YMRS scores, compared to previous reports [201], there was still a significant correlation between severity of mood symptoms and inflammation. This may indicate that inflammation is involved in some specific pathological mechanisms in BP. However, it cannot be ignored that inflammatory markers have a role in affect regulation also in SCH, since there was less variation in mood symptoms compared to the degree of other symptoms.

10.4 Large variation in immune markers

The analysis in present thesis showed that the variation in inflammatory markers were larger in patients than in controls. A large variation in inflammatory levels among patients, have been presented also in other studies, although this has not been commented by the authors [193, 197, 200, 263]. In the present study, OPG had higher variation among patients than controls. OPG has only been measured in two small previous psychiatric studies, including only 13 and 24 patients respectively. However, these two studies found opposite trends with respect to OPG levels in two samples of depressive patients differing with respect to having a history of anorexia [239, 240]. This suggests that different characteristics in subgroups of patients may explain some of the variation. Furthermore, a study found that there is a large variation in levels of polyunsaturated fatty acids (PUFA) among SCH patients [264]. Such PUFAs have been found to affect OPG levels [265, 266]. It has also been reported that there is a large unexplained variation in levels of

inflammatory markers in healthy persons [267]. A search for factors which may explain the large variation in inflammatory markers would therefore be interesting.

10.5 Affective state and inflammatory markers

10.5.1 High inflammation in bipolar disorder patients in manic state

BP patients in manic state had the highest levels of four inflammatory markers. They had higher levels of sTNF-R1 than controls, and depressed patients. TNF-R1 was also positively correlated with degree of elevated mood. The findings are supported by a recent study reporting higher levels of TNF-R1 in BP mania,than in BP neutral affective state and in controls [232]. In addition, three studies which measured TNF-α found elevated levels in mania [193, 197, 200]. BP manic patients also had the highest levels of OPG, IL-1Ra and vWf compared to the other states of BP. Nine previous studies one or more inflammatory markers were associated with mania [188, 192-194, 196-200]. To conclude, the findings of high inflammation in mania, is supported by other studies, and seems best substantiated for the TNF-pathway.

Although studies seem consistent in high inflammation in mania, this association is not in line with research on cytokine induced sickness behavior. It has been a well-accepted and much replicated finding in both animal and human research, that central inflammatory cytokines induces depressive mood, reduced energy and sleepiness. These are typical symptoms of infections, and many studies have shown that cytokines are mediators of these symptoms [189, 191, 268]. In line with this, TNF-blocking medication has been found to reduce the risk of depression in patients with autoimmune disease [269]. Other symptoms of mania, such as decreased need for sleep, increased energy and talkativeness are also quite opposite from symptoms in sickness behavior. It remains a puzzle why BP patients with high levels of inflammation have elevated mood.

10.5.2 Normal levels of inflammation in bipolar depression

Bipolar depressed patients had lower levels of inflammation than those in neutral state and manic state, and approximately equal levels as controls. They had non-significantly lower levels of IL-1β, IL-6 and hsCRP than controls. This was an unexpected finding, as unipolar depression has been associated with high levels of inflammation.

There are few published studies of bipolar depression, most with small samples. One study, however, reported high levels of TNF in 9 patients, another found high IL-1β in 10 patients, a third found high hsCRP in 30 patients [197, 198, 200]. Another reported that CRP was correlated with severity of depression in 30 bipolar depressed patients [198]. However, a recent study found equal levels of TNF-α in 24 depressive patients [201], another found equal levels of hsCRP in 20 bipolar depressed patients [199]. Importantly, the largest study so far, found no correlation between depression and inflammatory markers in 122 BP patients [192].

The current findings of low inflammation in depression and high in mania seems in also in line with a study reporting an inverse pattern of cytokine levels in mania and depression [200]. Thus, it seems as the findings in the present thesis is supported by some recent studies.

Many studies has found elevated levels of inflammation in major depression, but according to a new meta-analysis, there is only evidence of high TNF and IL-6 , while IL-1β is non-significantly lower [190]. Several studies have also reported low inflammation in depression. Studies have reported low IL-6, CRP [270-272], OPG [240], TNF and TNF-R1 [164, 270-275] in depression. A negative correlation between vWf and depressed mood has also been observed [238]. Furthermore, several studies has reported that that treatment effect of antidepressive medications is associated with increasing levels of TNF-R1 [276, 277], IL-6 [278, 279] and IL-1 [276, 277, 280], which supports that patients may have low inflammation in depressive state, that normalize into a higher level after treatment response. A recent review has described that depression seems characterized by both immune activation and suppression [281]. Further, unipolar and bipolar depression has differences in symptom profiles and pathophysiology [282]. This makes it is possible that bipolar depression is characterized by lower levels of inflammation than unipolar depression. More studies are needed to elucidate this possibility.

There were highly significant correlations between severity of depressed mood and low inflammatory markers in BP patients. The trend was similar for all markers, but was only significant for OPG, IL-1Ra and IL-6. The associations were significant for both the core depressive symptom sad mood, and for the total score on IDS. None of the previous studies in BP patients has reported such an association between severity of mood symptoms and serum markers. However, in one study, a negative correlation between degree of depression and sTNF-

R1 was found. The correlation coefficient was approximately as high as in this study, but as the study had included fewer patients, the association was statistically non- significant [232]. Nevertheless, the study that found a similar trend as in this theses supports that the findings of low inflammation in bipolar depression may be a valid result.

HsCRP and IL-6 were differently associated with affective state than the other markers. Patients in neutral state had higher levels of IL-6 than depressed and manic. According to a recent review, there is less evidence of elevated IL-6, than of TNF-α and IL-1β in severe mental disorders [188]. According to a new study, patients with low levels of IL-6 had good treatment response to anti-depressive medication, and treatment response was associated with increasing IL-6 levels [283]. Another study reported that high levels of IL-6 in depression were associated with poor treatment response [284]. These two studies seem to support that low levels of IL-6 may be a valid finding in depression. Furthermore, IL-6 has been found to be more associated with anxiety and irritability than with feelings of depression [285]. This suggests that high levels of IL-6 in some previous studies may have been caused by comorbid symptoms as anxiety and irritability, while the low levels in this study, could have been due to less anxious and irritable patients. .

10.6 Methodological issues

The current thesis has some limitations. The studies are cross-sectional, as most studies in the field of immunology in psychiatry, and this limits the discussion of causality.

Although the results were controlled for many confounders, it cannot be ruled out that confounding factors are present. Differences in smoking habits could be such a confounder, but smoking were not significantly correlated to the inflammation markers. Furthermore, it has been shown that smoking cessation does not change the levels TNF-RI or vWf [286]. OPG has been reported to be low in smokers, supporting that the high OPG in patients is not caused by smoking.

Antipsychotic medication has been associated with both inflammatory and anti-inflammatory effects [287, 288]. However, in the present study, there was no difference in inflammation between medicated and unmedicated patients. This is in line with a recent review, where it was concluded that markers as TNF-α was not significantly affected by antipsychotic treatment [235].

Furthermore, despite different drug regimens, the two diagnostic groups showed similar profiles of inflammatory parameters.

It cannot be ignored that the present results may be affected by differences in non-fasting status [167]. However, this is not likely since the results were controlled for many factors that usually are associated with fasting status. Furthermore, as shown in table 1, study III, patients in this study did not have elevated levels of glucose, and triglycerides. It is not likely that any differences in fasting status have had any large impact on levels of inflammatory markers, when not having impact on glucose and triglycerides.

It is a possibility that some patients may have a shift in affective status between time of clinical assessment and blood sampling. However, the duration of mood episodes is usually long, with a median length of 3 months and even after remission, the symptom profile tend to have similarities with the polarity of last affective episode [58, 289]. This makes it unlikely that affective shift had any major influence on the results.

It is also unlikely that differences in autoimmune disease could explain the study result, because having a diagnosis of autoimmune disease was not significantly associated with higher levels of inflammation. Furthermore, the low inflammation in the BP depression could not be due to autoimmune diseases, as the frequency of autoimmune diseases was equally distributed in the affective groups.

Patients did not have significantly higher IL-1Ra, which is in contrast to a recent review reporting high IL-1β in patients. However, this study measured IL-1Ra instead of IL-1β. A rather low correlation between IL-1β and IL-1Ra measurements has been reported in one study[209]. Moreover, IL-1β circulates at low levels just above the detection limit of various assays, and thus IL-1Ra is regarded as a more stable and reliable marker of the activity in the IL-1 system, better than IL-1β itself. TNF-R1 is also regarded a more stable and reliable marker than TNF-α [203, 210], which could explain why this study had very significant elevations.

In addition, differences regarding sample size, disease severity and comparison groups makes it difficult to compare the studies [167]. This current study is the largest so far. In addition, we

controlled the results for more possible confounders than previous studies. This reduces the risk that the associations are a result of chance findings.

10.7 Underlying mechanisms

10.7.1 Possible factors leading to high TNF

10.7.1.1 Genetic factors

It is still uncertain which genetic factors that influence serum levels of TNF-R1 in clinical samples [290]. In a large whole genome study, the five top genetic susceptibility loci were in the extended MHC region. The gene for TNF-α is the only cytokine, which also lies in the extended MHC region. This region has strong linkage making it difficult to evaluate the impact of any single gene, as many genes are often inherited together [107]. NOTCH4 is a MHC gene associated with risk of severe mental disorders. This gene is regulated by TNF-α [254]. In addition, the susceptibility gene PLAA [291] influences TNF-α expression [292]. The complement controlled gene CSMD1,has also been associated with SCH [293], and this gene is associated with susceptibility to several viral infections [294]. Thus, it is possible that genetic factors could be a cause of high TNF-R1.

10.7.1.2 Autoimmune reactions

The analysis in this theses found no evidence that high TNF-R1 in patients is due to autoimmune diseases. Still, it is possible that autoimmune processes could be a cause of high inflammation. Autoimmune reactions can occur in all organs, including the brain, and autoantibodies to different types of brain molecules has been reported in SCH [295]. High levels of autoimmune antibodies has also been found in their serum [15, 296]. As high TNF is is a typical characteristic of autoimmune diseases, it may be undiagnosed autoimmune processes which contribute to high inflammation in patients.

10.7.1.3 Mental stress

High levels of interpersonal stress have been found predictive of high inflammation [297]. Patients with severe mental disorders are vulnerable to mental stress, and to critical comments and negative communication with family members [298]. This type of communication has been found to induce increased levels of TNF-α [299]. Furthermore, psychological stressors and immune challenges may have synergistic effect on the induction of inflammatory markers [151].

10.7.1.4 Neurotropic infections

Viruses in the herpes family are the ones which most consistently has been associated with increased risk of SCH. Herpes viruses are neurotropic and reside within cells in a latent phase. This means that when first infected, the person is infected for the rest of his life. Approximately 70% of adults have been infected with HSV1 [102]. HSV1 infects the face, gets access directly to the brain stem through the fifth brain nerve, and commonly resides within the trigeminal ganglion in the brain stem, which is a region affected in severe mental disorders [94]. A study investigating TNF-α expression in neurons infected by HSV1, found TNF-α expression in nearly 100% of of the trigeminal neurons. In contrast, TNF-α was not detected in neurons free of HSV1 [300]. It could be speculated that if there are more neurons infected in patients, it could probably induce higher levels of TNF-α.

From the brain stem, HSV1 may reactivate from its latency and infect the brain causing encephalitis. In such cases it preferentially affects the temporal cortex and limbic structures [301]. An acute infection increases dopamine transmission [302] and typical symptoms are headache, personality changes, hallucinations, cognitive disturbances, impaired consciousness and convulsions [303]. Although an acute infection resolves rapidly, it may induce progressive brain morphological changes including increased brain ventricle sizes [304, 305]. It mainly infects limbic structures as the hippocampus [305]. An acute HSV encephalitis infection may show no signs of infection in the cerebrospinal fluid [305] and a rise in antibody titers cannot be used to detect reactivations of the viruses [103]. The ability to induce pathological disturbances seen in severe mental disorders, make them therefore difficult to detect.

In line with this, a small post-mortem study found HSV in 4 out of 6 hippocampus samples from SCH patients. None of them have had any known encephalitis [306].

As mentioned, antibodies to HSV1 has also been associated with poorer cognition and smaller brain volumes in BP and SCH and an association between HSV1 and cognition has also been found in healthy persons [46-48, 50, 51, 97, 307, 308].

Another cause of high TNF- α may be cytomegalovirus. This virus is associated with risk of SCH [309, 310] as well as with increased levels of TNF-α. [311]. Cytomegalovirus preferentially infects glial cells and macrophages in the brain, but neurons may also be infected. In line with this, cytomegalovirus has also been found to induce neuronal death [311]. Cytomegalovirus may be difficult to detect, as infected neurons may not show any antigens [311, 312].

10.7.2 Possible factors leading to high vWf and OPG

10.7.2.1 Genetic factors/neurotransmitters.

One factor that possible can participate in the increased vWf and OPG levels may be genetic. The CACNA1c is a much replicated susceptibility gene [241]. The gene encodes a calcium channel with immune modulating effects [313], and regulates the expression and secretion of OPG [314]. Thus, it could be speculated that high OPG levels may be caused by genetic variants in the CACNA1c gene. The CACNA1c channel contains a domain consisting of vWf. This domain is a key regulator of influx though the channel [315]. In addition, the cleavage of vWf has recently been found to be influenced by calcium [258]. VWf has a calcium-binding site that regulates its cleavage. It makes it possible that high vWf may be due to genetic susceptibility [258]. In addition, the complement related susceptibility genes CSMD 1 and 2 could be a cause of high vWf [293], as the complement cascade increases release of vWf [105]. Another newly discovered susceptibility gene called NOTCH4 may also be a cause of high vWf, as it is associated with endothelial dysfunction [254, 255].

High levels of vWf may also be caused by changes in monaminergic neurotransmission as the release of vWf is increased as response to epinephrine, and is inhibited by dopamine [316].

10.7.2.2 Neurotropic patogens

VWf is expressed at higher levels in endothelial cells infected with the cytomegalovirus infection [317, 318], which makes it likely that cytomegalovirus, as a risk factor of severe mental disorders, may be one possible cause of high levels of vWf [37]. Cytomegalovirus antibodies has been found predicative of high vWf levels as long as 15 years after the first measurement [319]. This supports that even fetal infection which is associated with increased risk of SCH, may induce high levels of vWf [320, 321]. That this may be an underlying cause of vWf is therefore potentially important.

HSV could be speculated to be a cause of high calcium related inflammation, as it harness calcium signaling to facilitate viral entry [322].

10.7.3 Possible factors underlying high inflammation in mania

High inflammation induces sickness behavior, which is characterized by opposite behavior from those seen in mania. It is a puzzle why BP patients with high inflammation have elevated mood, when the typical is to have reduced mood. One possible mechanism may be that it due to

interactions with pathogens. Herpes, cytomegalovirus and toxoplasma tend to increase dopamine levels [302, 323]. Dopamine neurons is mediators in the reward system, and increases the feelings of pleasure [324]. It is possible that the pathogens increase dopamine levels, and thereby causes a feeling of elevated mood, as well as inducing high levels of inflammation [325].

10.7.4 Possible causes factors underlying low inflammation in depression

It was a somewhat unexpected finding that depressive state of BP had the lowest levels of inflammation. It could be speculated if this is related to levels of catecholamine neurotransmitters which has been reported to be low in depression and high in mania [326]. High levels of catecholamines (norepinephrine and dopamine) have been found to increase inflammation, and vice versa [327, 328]. However, these neurotransmitters have also been reported to have immune suppressive effects [329]. Not only do neurotransmitters influence cytokines, it is also the opposite way around [330-332]. Thus, it is still unclear how the immune system interacts with neurotransmitters. The interaction may be influenced by many unknown factors making it difficult understand the mechanisms.

Although acute stress may cause elevated inflammation, long-term psychosocial stress has been found to lower inflammation [333, 334]. The mechanisms involved are complicated and how the stress influences immune responses may vary, and depending on many factors as i.e. timing. Thus, it is possible that low levels of inflammation in depressed BP patients may be related to long-term psycho-social stress.

Although pathogens associated with severe mental disorders may cause high inflammation, they also have some immune suppressing effects [335-337]. They may also have specific immune modulating effects, elevating some cytokines, while inducing a restricted reduction of others [338]. Furthermore, when the immune defence fights the neurotropic infections in cathecholamine producing neurons, it may result in a reduced number of catecholamine producing neurons. This mechanism has been suggested as a cause of high risk of depression following HSV encephalitis [339].

10.7.5 Possible consequences of high TNF-R1, vWf and OPG

10.7.5.1 Cognitive impairment

Cognitive impairment is an important predictor of poor treatment outcome in patients with severe mental disorders, and experts have suggested that improving cognitive function should be a treatment target [10, 71, 72]. Therefore, it is of importance that high levels of TNF-R1 induce cognitive impairments in animals, and are predictive of cognitive impairment in humans.

Many animal studies have found that high levels of systemic inflammation induces neurodegenerative effects in the brain [340], and that high TNF induces detrimental effects on cognition [154]. The impact on longstanding elevations in TNF may be substantial, as a high level of TNF-α for 100 days has been found to induce neurodegeneration and loss of 75% of the dopamine neurons in the striatum of mice [341]. The apoptosis inducing domain of TNF-R1 has been found to mediate neurodegenerative processes in an animal model of dementia [116], and medication which specifically reduce the TNF-R1 signaling has been suggested as treatment for neurodegenerative diseases [155].

In line with the animal studies, high levels of TNF / TNF-R1 has been found predictive of cognitive impairment in humans. In a study of 1037 healthy older persons, those with high TNF-α had poorer cognitive abilities [342]. In a study of 691 healthy individuals those who had higher TNF-α had an increased risk of cognitive decline during the next years [158]. In line with this, a study of 1430 healthy persons found that high levels of TNF-α was associated with smaller brain volumes [343]. TNF-R1 has also been found to correlated with a marker of axonal damage called tau in both healthy persons and patients with mild cognitive impairment [205]. The levels of TNF-α and TNF-R1 has also been found predictive of further cognitive decline in patients with mild cognitive impairment [205, 344]. In those who already have dementia, acute systemic inflammatory events with high TNF-α dramatically increased the rate of cognitive decline over a 6-months period. In contrast, patients who had low levels of serum TNF-α throughout the study showed no further cognitive decline [345]. To summarize, high TNF-α /TNF-R1 has been found to induce memory impairment in animals, and to be predictive of memory impairments in healthy persons, in persons with mild cognitive decline and in those with dementia. Thus, it seems reasonable to assume that also in patients with severe mental disorder, high levels of TNF-R1 will imply risk of memory impairment.

10.7.5.2 Risk of cardiovascular disease

Each of the inflammatory factors vWf, TNF-R1, OPG, hsCRP and IL-1Ra is associated with increased risk of cardiovascular disease and coagulation disturbances [171, 346-348].

HsCRP has been much investigated as a risk factor of cardiovascular disease [102]. The risk associated with high hsCRP, has been found independent of the risk associated with high sTNF-R1, vWf and OPG [171, 184, 347]. VWf was reported to be more predictive of both cardiovascular disease and of mortality from all causes, than hsCRP [171]. In addition, TNF-R1 has been reported to be more predictive of CVD mortality than hsCRP. In two prospective studies, including 660 and 1400 patients, sTNFR1, but not hsCRP, was independently associated with pathological heart changes and mortality [347, 349]. Furthermore, a quite new study including 1400 persons found that TNF-R1 was predictive of CVD mortality independent of other factors [290].

OPG has been investigated in more than 300 studies related to cardiovascular disease. It has been associated with prevalence and severity of coronary artery disease, cerebrovascular disease and peripheral vascular disease, and to be predictive of mortality in different populations and disease categories. Circulating OPG levels are increased in patients with acute coronary syndrome. Enhanced expression has been found within symptomatic carotid plaques and OPG has been reported to predict survival in patients with heart failure after acute myocardial infarction, to predict heart failure hospitalization and mortality in patients with acute coronary syndrome. It is also associated with long-term mortality in patients with ischemic stroke [184]. It is previously reported that OPG levels, comparable to those found in the patients group in the present study, (above 2.3 – 2.9 ng/ml) are associated with increased cardiovascular morbidity or mortality in patients with stroke or acute coronary syndrome [350, 351]. Also in the general population, elevated OPG levels have been associated with the degree of coronary calcification as a marker of coronary atherosclerosis. Importantly, OPG has been found predictive of cardiovascular disease, independent of traditional risk factors in a large population based study, investigating healthy individuals, and also after control for traditional risk factors for cardiovascular disease [352].

The good properties of OPG as a marker of CVD has been suggested to be due to its properties as a stable marker of activity in the RANKL/OPG/RANK axis, as well as it is thought to mirror the

activity in pathways with relevance to atherosclerosis, as inflammation and vascular calcification [184].
This means that the inflammatory profile found in this theses, strongly suggests that patients have elevated risk of cardiovascular disease.

11 Generalizability of results and implications for further research.

11.1 Generalizability of the current results

The patients in the study are included from a catchment area, and are assumed representative for the average patients receiving treatment at this level. The study has the also the advantage of having a large sample size. According to this, it could be assumed that results are generalizable to other clinical samples of patients with the same diagnosis.
The selection of patients in the study is probably slightly better functioning patients, understanding the importance of contributing to research. However, this is a general problem in clinical studies that depend on informed consent.

11.2 Implications for further research

Immunosuppressive medications as Non Steroid Anti Inflammatory Drugs (NSAID), Aspirin and TNF-inhibitors have been suggested as treatment for patients with severe mental disorders [353, 354]. Some placebo-controlled trials have also found anti-inflammatory drugs effective as adjunctive therapy against SCH and BPs [355, 356]. However, there was a large variance in inflammatory levels among patients. Especially bipolar depressed patients did not have elevated levels. They will probably not benefit from further reductions of the inflammatory mediators. Furthermore, there is a possibility that anti-inflammatory medications will have a negative effect in patients who have neurotropic infections. Moreover, lithium has been found to increase TNF in healthy persons and to have immune stimulatory effects [99, 357].

Further research is needed to find out what causes the increased inflammation, and if there are patients with specific symptoms of inflammatory profile who will benefit from adjunctive treatment with anti-inflammatory medications.

Patients with severe mental disorders have reduced brain volumes, and cognitive impairments, [32, 358]. As TNF has been associated with both cognitive impairments and reduced brain volume, further research is needed to find out if patients with high levels of TNF-R1 are more cognitively disturbed and at risk of cognitive decline. Longitudinal studies investigating if levels of inflammatory markers normalize in remission and if levels fluctuate depending on relapse of affective symptoms are needed. Further studies on whether symptom profile and comorbid diseases may explain variation in inflammation are also needed.

12 Conclusions

The theses aimed to increase the understanding of the role of systemic inflammation in severe mental disorders. The major conclusions are as follows:

- The investigations determined levels of inflammation in patients with severe mental disorder and found that they have highly significant elevations, also after controlling for many confounding factors.
- The results indicate that specific inflammatory pathways were disturbed. There were specific elevations in the general inflammatory marker TNF-R1, in the endothelial related von Willebrand factor and in the calcium related marker OPG.
- The inflammatory profile does not differ between patients with BP and SCH.
- The study found that inflammatory markers were associated with affective state. BP patients with elevated mood had the highest levels of inflammatory markers and bipolar depressed patients had the lowest.
- Severity of depression was inversely correlated with inflammation, which was significant for IL-1Ra, IL-6 and OPG.

The results show that inflammatory disturbances are of importance in severe mental disorders and suggests that they may be involved in abnormal affective regulation in BP.

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13 Errata

In table 1, study II, it says that No of controls smoking were Zero (0), but the correct should be missing (-).

14 Full text articles of study I, II an II

I

II

III

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