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PSYCHIATRIC COMORBIDITY IN MULTIPLE SCLEROSIS – BIOLOGICAL AND EPIDEMIOLOGICAL ASPECTS

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"A man who wants the truth becomes a scientist; a man who wants to give free play to his subjectivity may become a writer; but what should a man do who wants something in between?"

— Robert Musil, The Man Without Qualities

ABSTRACT

Multiple sclerosis (MS) is a chronic, neuroinflammatory disease and one of the leading reasons for neurological disability among young people in the Western World. MS patients commonly experience neuropsychiatric symptoms including depression and cognitive dysfunction.

The aims of this thesis were to (study I-III) epidemiologically study the occurrence of common psychiatric diagnoses and their consequences, such as disability pension (DP) and suicide, among MS patients, and (study IV) examine the association between inflammatory biomarkers, depression and stressful events in a clinical cohort of MS patients.

For studies I-III, Swedish national and clinical registers were used to identify patients with MS from the 1960s to 2012 (n=10,750- 29,617) and non-MS comparison subjects, as well as several covariates including sociodemographic data, disability pension, psychiatric diagnoses, prescriptions of psychiatric drugs, and attempted and completed suicide. Statistical analyses estimated the adjusted risks for a) having psychiatric diagnoses, b) the risk for being granted DP if having a psychiatric diagnosis, c) the prescription patterns of selective serotonin reuptake inhibitors (SSRIs), benzodiazepines and sleeping medications in the years around DP, and d) the risk for attempted and completed suicide.

For study IV, 47 patients with MS in a clinical setting were assessed using self-rating scales and clinical interviews regarding symptoms and diagnosis of depression, and exposure to violence in childhood or adult life. Cerebrospinal fluid (CSF) interleukin (IL)-6 and -8 levels were analyzed and compared with results from the psychiatric ratings.

In study I-III, MS patients were at higher risk for having most psychiatric diagnoses and medications compared to non-MS subjects. MS patients with psychiatric diagnoses or medications had a higher risk for DP compared to those without. MS patients with DP had a higher risk for prescription of SSRIs and benzodiazepines than non-MS subjects with DP. MS patients had a nearly doubled risk for both attempted and completed suicide. In study IV, higher IL-6 levels were associated with depressive symptoms and exposure to violence in adult life, while IL-8 levels were not associated with any investigated parameters.

We conclude that MS patients are at risk for psychiatric comorbidity, with increased rates of serious consequences such as DP and attempted and completed suicide. Furthermore, DP is not associated with a decrease in psychiatric drug prescription, as in non-MS patients. Also, both depressive symptoms and exposure to violence were associated with an inflammatory biomarker in CSF in MS patients, further establishing the association between neuroinflammation, psychiatric symptoms and exposure to stress.

LIST OF SCIENTIFIC PAPERS

I. **Brenner P**, Alexanderson K, Bjorkenstam C, Hillert J, Mittendorfer-Rutz E, Tinghög P. Psychiatric diagnoses, medication and risk for disability pension in multiple sclerosis patients; a population-based register study. *PLoS One*. 2014 Aug 5;9(8):e104165. doi: 10.1371/journal.pone.0104165

II. **Brenner P**, Mittendorfer-Rutz E, Jokinen J, Alexanderson K, Hillert J, Tinghög P. Prescribed psychiatric medication among multiple sclerosis patients before and after disability pension: a register study with matched controls. *Social Psychiatry and Psychiatric Epidemiology*. 2016 Jul;51(7):1047-54.

III. **Brenner P**, Burkill S, Jokinen J, Hillert J, Bahmanyar S, Montgomery S. Multiple sclerosis and risk of attempted and completed suicide - a cohort study. *European Journal of Neurology*. 2016 Aug;23(8):1329-36.

IV. **Brenner P**, Granqvist M, Königsson J, Al Nimer F, Piehl F, Jokinen J. Cerebrospinal fluid immunomarkers in multiple sclerosis; relationship with stress exposure and severity of depression. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

5-HIAA	5-hydroxyindoleacetic acid
5-HT	Serotonin
BDI	Beck Depression Inventory
BVMT-R	Brief Visuospatial Memory Test
CESD	Center for Epidemiologic Studies Depression Scale
CI	Confidence Interval
CNS	Central Nervous System
CVLT-II	California Verbal Learning Test, Second edition
DDD	Defined Daily Dosage
DP	Disability pension
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion Tensor Imaging
EAE	Experimental Autoimmune Encephalomyelitis
EDSS	Expanded Disability Status Scale
GEE	General Estimating Equation
HAD	Hospital Anxiety and Depression Scale
HPA	Hypothalamic-pituitary-adrenal
HR	Hazard Ratio
IDO	Indoleamine-2,3-dioxygenase
ICD	International Statistical Classification of Diseases and Related Health Problems
IFN-β	Interferon-beta
IFN-Υ	Interferon-gamma
IL	Interleukin
IR	Incidence Rate
KIVS	Karolinska Interpersonal Violence Scale
KYN	L-kynurenine
KYNA	Kynurenic acid
MADRS-S	Montgomery-Asberg Depression Rating Scale, Self-report version

MDD	Major Depressive Disorder
M.I.N.I.	Mini International Neuropsychiatric Interview
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Multiple sclerosis
NBHW	National Board of Health and Welfare
NDMA	N-Nitrosodimethylamine
NPR	National Patient Register
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire-9
PPMS	Primary Progressive Multiple Sclerosis
PRMS	Progressive-relapsing Multiple Sclerosis
QUIN	Quinolonic acid
RA	Rheumatoid Arthritis
RRMS	Relapsing-remitting multiple sclerosis
SDMT	Symbol-Digit Modalities Test
SLE	Systemic Lupus Erythematosus
SPMS	Secondary Progressive Multiple Sclerosis
SSRI	Selective Serotonin Reuptake Inhibitors
Th	T-helper
TNF-α	Tumour necrosis factor-alpha
WCST	Wisconsin Card Sorting Test

1 BACKGROUND

1.1 MULTIPLE SCLEROSIS

1.1.1 Introduction

Multiple sclerosis (MS) is a chronic, autoimmune inflammatory disease of the central nervous system (CNS). As such, it can cause a wide variety of neurological symptoms, ranging from movement and sensory to cognitive disabilities. MS is described as the leading cause of neurological disability among young and middle-aged people in the Western world. With onset most commonly in early adult life, MS can have a detrimental impact on several aspects of life.

The main focus of this brief overview of the literature will be on psychiatric aspects of the disease, reviewing biological and epidemiological evidence and the association with occupational disability. Although this thesis does not focus directly on the areas of cognitive dysfunction or fatigue, these areas will be covered for completeness due to their complex interplay with depression.

1.1.2 Epidemiology

The global mean prevalence of MS is 33/100,000, but with considerable variation[1]. Prevalence is highest in North America and Europe, with Sweden being the European country with the highest reported prevalence (189/100,000)[1]. A north-south gradient has been suggested, and questioned[2], but seems to be confirmed in some later studies, at least in the Western hemisphere[3,4].

The female to male ratio of MS ranges from 2:1 to 3:1, and it is unclear whether this ratio has increased over time[3,4]. Although MS can be diagnosed at any age, the average age of onset is 30 years[1]. An approximate 2-5% of patients are diagnosed under the age of 18[5].

1.1.3 Pathology

MS pathology is characterized by an autoimmune inflammatory response targeting myelin, a lipoprotein manufactured by oligodendrocytes which normally forms a sheath around axons of neurons[6]. The characteristic lesions of demyelination and inflammation ("plaques") that can be observed radiologically and post mortem are often found in a periventricular white matter distribution, as well as in the corpus callosum, the optical nerve and the spinal cord. Lesions are categorized into active, inactive or chronic active depending on inflammatory activity and histological cell content; i.e., the activation of macrophages and CD4+ and CD8+ T lymphocytes. Cortical demyelination and general atrophy are often prevalent especially in progressive disease stages[7]. Disease progression is mediated by accumulated axon degeneration[8].

1.1.4 Etiology

The etiology of MS is largely unknown, but genetic and environmental risk factors have been proposed. More than 100 associated genetic risk variants have been identified[9], and siblings to MS patients have a somewhat increased risk for the disease[10]. Vitamin D deficiency/sunlight exposure[11], Epstein Barr-virus infection[12] and cigarette smoking[13] have all been associated with MS, which could be explained by their respective immunomodulating properties.

1.1.5 Diagnosis and clinical sub-types of MS

The current criteria for diagnosis of MS, the so-called updated McDonald criteria, consist of clinical and laboratory parameters aiming to demonstrate dissemination of CNS lesions in time and space[14]. The most commonly used division of MS into sub-types is based on the clinical course[15]. Of newly diagnosed patients, 80% suffer from relapsing-remitting MS (RRMS)[1], characterized by exacerbations of neurological symptoms followed by complete or partial recovery. Of these patients around 90% will in time develop secondary progressive MS (SPMS), meaning irreversible and/or progressive disability[16]. About 10% of patients have a primary progressive form (PPMS) at disease onset[17]. Rarely diagnosed, progressive-relapsing MS (PRMS) is characterized by ongoing progression from onset which is superimposed by clinical relapses.

1.1.6 Clinical features

The symptoms of MS generally correspond to the location of lesions, which means that presentation can vary widely. Common onset symptoms include limb weakness, optic neuritis, paresthesias or dysesthesias, ataxia, diplopia, facial numbness, vertigo, dysarthria, marked fatigue and urinary dysfunction. About 80% initially present a single symptom (clinically isolated syndrome, CIS) and thus do not yet meet criteria for MS. The rate of new exacerbations seldom exceed 1.5 per year[8]. The clinical course usually evolves over several decades, with a median time of 28 years relapsing before patients require at least a cane for walking[18]. Cortical signs such as aphasia, apraxia, seizures, dementia and extrapyramidal symptoms are more common in progressive disease, as is optic nerve and brain stem pathology[8].

MS patients' life expectancy is 5-10 years lower than the general population[19]. Among the common causes of death are general consequences of neurological disability such as infections and cardiovascular complications[20].

1.2 PSYCHIATRIC COMORBIDITY IN MS

Although well known since MS was first described in the 19th century[21], the psychiatric symptoms of MS have been little investigated up until the last three decades, following the

development of standardized psychiatric diagnostic frameworks and advancements in the field of neuropsychology.

1.2.1 Comorbidities or symptoms?

There are two conceptually different ways of viewing psychiatric symptoms in MS patients - as symptoms of the disease itself, or as symptoms of a comorbid psychiatric disorder. There is no consensus on this matter in current literature, and the viewpoint chosen seems to vary depending on which symptom/comorbidity is studied, and the setting in which the study is performed.

The concept of comorbidity has several definitions in itself, depending on the environment in which the constructs are applied (e.g. clinical care, epidemiological research, or health service planning or financing)[22]. Different diseases may be found in the same individual for several reasons: chance, selection bias, or by one or more types of causal association[22]. The latter may be divided into four models: direct causation, associated risk factors, heterogeneity (=independent risk factors), and independence (the presence of diagnostic signs of both diseases is actually due to a third, underlying disease)[23].

In the MS literature in general, symptoms of a more typical neurological character and those which are almost exclusively seen in patients with neurological disease, such as pseudobulbar affects (see section 1.2.6) are commonly labeled "neuropsychiatric symptoms". Conditions that are common also in patients without neurological disease, such as depression, and those who tend to be associated with psychosocial reactions, e.g. anxiety, are more often labeled "comorbidities".

1.2.2 Depression

Depression is the most studied psychiatric condition in MS patients. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition[24], depression is defined as a medical diagnosis under the name major depressive disorder (MDD), and is constituted by a combination of depressed mood and/or loss of interest or pleasure, persistent over at least two weeks, in combination with cognitive (feelings of worthlessness or guilt, disturbed concentration, suicidal thoughts) and/or vegetative (weight loss or gain, insomnia/hypersomnia, agitation or retardation, fatigue) symptoms. The estimated prevalence in MS patients varies widely depending on the definition of depression, the study sample and the methods used, but is according to a meta-analysis around 24% in population-based studies[25], around three-fold that of the general population. The one-year incidence in a clinical sample was 3-10%[26]. In a German claims data study, 20% of MS patients were prescribed an antidepressant medication during a single year[27]. Risk factors for depression in MS patients may include lower level of education and being unmarried[26] as well as being female[28]. Compared to matched controls from the general population, male MS patients have a higher burden of depression and anxiety than females[29].

Depression can have a detrimental impact on the MS disease in several ways. It is, together with physical disability, the most important factor in determining MS patients' quality of life[30-32]. It is also associated with a higher rate of hospitalizations[33] and lower adherence to disease modifying therapy (DMT)[34]. Some studies have shown an association with an early disease course [35], and others with advanced disease[26]. There is also an association with relapses[36]. In SPMS patients, e.g. after years of disease, feelings of hopelessness become more common[37]. In a cohort of MS patients with depression, symptoms were unchanged or only slightly decreased in a four-year interval, suggesting a chronic course[38].

MDD is a clinical diagnosis, but various self report scales exist for the purposes of screening, symptom severity rating, and assistance in diagnosis. Two screening questions, corresponding to the MDD core symptoms of depressed mood and loss of interest, may detect depression with reasonable sensitivity and specificity in MS patients[39]. The Beck Depression Inventory (BDI)[40]is a well-established 21-item measure, of which both the original[41,42] and a 7-item version[43] have been validated for MS patients. The Hospital Anxiety and Depression scale (HAD)[44] is designed for depression and anxiety assessment in somatic patients, and has also been validated for MS patients[41,45]. A recent comparison between several self report measures[46] showed that none of the measures used identified depression with adequate accuracy, although the Center for Epidemiologic Studies Depression Scale (CES-D)[47] and the widely used Patient Health Questionnaire-9 (PHQ-9)[48] showed better detection performance using optimal cut-offs, while another comparative validation study found that the PHQ-9, HAD and CES-D all performed reasonably well[49].

There is an overlap between some depressive symptoms and certain common MS-related symptoms such as fatigue, insomnia and cognitive dysfunction. This has caused debate regarding both the validity of the diagnosis of MDD in MS patients and the conceptualization of comorbidity vs inherent neuropsychiatric symptom[50]. Conceptual models of depression in MS have tried to incorporate biological signs such as neuroinflammation as well as psychosocial factors (i.e. psychological impact of disability, lowered socioeconomic status)[51]. Psychosocial factors have been shown to explain 40% of variance in patients' self-reported depression[52]. However, a temporal relationship between MS diagnosis and MDD was not present in one public health register study, arguing that it cannot be solely explained by a psychological reaction to the diagnosis[53]. MDD episodes are more common among MS patients than time-matched controls before the MS diagnosis[53,54], as are SSRI prescriptions[55]. Omitting the overlapping somatic symptoms from rating scales for depression has been proposed[56], but this concept has also been criticized for missing vital components of depressive symptomatology that can actually improve when MS patients are treated for depression[57]. Importantly, the clinical phenotype of depression does not seem to differ substantially when comparing MS and non-MS MDD patients[58].

Several brain imaging studies have shown associations between depression and MS morphology; however, results are diverse and sometimes conflicting. In conventional

magnetic resonance imaging (MRI) studies, multiple measures of brain pathology such as lesion load, lesion distribution and brain atrophy have been shown to be associated with depression, and could explain up to 40% of depression variance[59]. Lower hippocampal volume has been associated with depression[60], and has also been shown to be associated with higher cortisol levels in depressed MS patients[61]. Newer techniques such as diffusion tensor imaging (DTI) show that subtle changes in both white and grey matter can be associated with depression in MS patients[62], as can various abnormal communications within the limbic systems[63]. In functional MRI, individual differences in depression were associated with altered regional activity and functional connectivity patterns within the limbic system[64].

1.2.3 Suicide

The most important potential consequence of depression is suicide. The literature as a whole demonstrates an elevated suicide risk among MS patients; however, estimates range from no risk elevation at all[65] to 14 times that of the general population[66]. Adequately powered population based register studies show more uniform results with an about doubled suicide risk compared to the general population[67-69]. In a large Swedish hospital sample, the highest suicide risk was found in the first year following discharge. Of suicides, 58% occurred within 5 years after the first admission[68]. The risk for attempted suicide has been investigated in only two studies, one of which showed a three-fold risk increase in MS patients[70], and one which did not show any elevated risk[71], but the latter was probably underpowered (MS patients n=404). Thoughts of death and self-harm in MS patients are associated with illness severity, depression, quality of life, male sex, and being unmarried[72]. The relationship between disability status and suicide ideation is, however, not clear; in one study, depression predicted suicidal ideation, while disability status did not[73] and in another, depression mediated the relationship between disability and suicidal ideation[74]. In another study, suicidal thoughts were present in 8% of community patients, and were more common in patients over 65 years of age and with bladder or bowel symptoms, or speaking or swallowing difficulties[75].

1.2.4 Cognitive dysfunction

Since pivotal studies in the 1990s revealed that at least 40% of community dwelling MS patients suffer from cognitive dysfunction[76,77], a substantial amount of research has been dedicated to this field. Cognitive dysfunction is one of the major causes of social and occupational impairment among MS patients[78,79]. Cognitive performance may be affected years before MS diagnosis[80].

The cognitive domains most commonly affected are attention and information processing speed, learning and memory, and executive functions. Attention and information processing speed is perhaps the most central domain in cognitive dysfunction in MS, and may also impact on other aspects of cognition[81]. The most widely used test for assessing information processing speed in MS patients is the Symbol-Digit Modalities test (SDMT)[82] which has

consistently proved to be a sensitive screening test for cognitive dysfunction in MS patients[76,83].

Memory seems to be one of the most affected cognitive domains in MS patients[84]. Particular difficulties is seen in encoding, rather than recalling[85,86]. As both visuospatial and verbal learning is affected, current expert panels' suggestions for brief screening tests[87] suggest that both the California Verbal Learning test, second edition (CVLT-II)[88] and the Brief Visuospatial Memory Test – revised (BVMT-R)[89] are administered when screening for cognitive dysfunction. Either test takes, like the SDMT, only a few minutes to administer.

Executive function refers to a complex set of abilities including planning, analysis and problem solving, abstract thinking, response inhibition and overall management of cognitive resources[84]. The most common test for evaluating executive function is the Wisconsin Card Sorting Test (WCST)[90] and, more recent, the Sorting Test[91]. MS patients have been shown to have difficulties completing projects and adapting to new situations[92]. Executive dysfunction has traditionally been associated with frontal lobe pathology, e.g. lesions[93], but the relationship is not at all clear [94] which is consistent with newer evidence of more complex cerebral pathways regulating executive function[95,96].

The relation between cognitive dysfunction and MS disease sub-types is not entirely clear. RRMS and PPMS/SPMS patients have different cognitive profiles[97], and progressive subtypes have been shown to be more frequently and seriously impaired[98], but this could be mediated by brain lesion load[99] and brain atrophy[100]. Interestingly, in a study of patients with a so-called benign course (at least 15 years of disease with a score on the Expanded Disability Status Scale (EDSS)[101] ≤3), 45% were cognitively impaired[102]. In cross-section studies, there seems to be no connection between duration of illness and cognitive dysfunction[76]. Long-term follow-ups, however, have shown significant worsening of cognitive dysfunction over time[103,104]. The relation to physical disability is also unclear, with some studies leaning towards an association[76,105].

The refinement of MRI techniques have coincided with a substantial literature showing correlations between MRI indices and cognitive dysfunction, such as regional and total lesion load detected by T1 and T2 weighted MRI[106], juxtacortical lesions[107], and regional and generalized atrophy[108]. The latter is perhaps the most important cerebral predictor of cognitive dysfunction. DTI studies have shown correlation between indices of normal appearing brain tissue and cognitive dysfunction[109]. Also, functional MRI studies have shown that cerebral adaption to cognitive deficits is possible by increasing activity in other brain regions[110]. However, this ability is limited by the extent of brain pathology[111].

1.2.5 Fatigue

Fatigue is the most commonly reported symptom among MS patients[112]. It affects up to 80% of patients[113] and is for many the most disabling symptom[114].

MS fatigue has been described as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual or desired activities"[115]. Attempts to define the concept in a medical context has been made[116], emphasizing that it is reversible, can impair both motor and cognitive functions, can appear spontaneously or be brought on by mental or physical activity, humidity, acute infection and food ingestion. It is usually worse in the afternoon.

Fatigue is more common in progressive forms of MS than in RRMS[117]. Most studies have not noticed any differences between the sexes[118].

Using conventional MRI techniques, lesion load does not seem to be strongly correlated to fatigue[119], but DTI shows a possible contribution of grey matter pathology[120]. Both global[121] and regional[122] brain atrophy has been associated with fatigue.

1.2.6   Anxiety and other psychiatric problems

The literature on anxiety in MS patients is small compared to that on depression, cognitive dysfunction and fatigue. Yet, preliminary research, both clinical and epidemiological, has shown that anxiety may be as common, if not even more so, than depression in MS patients[123,124]. Regarding specific anxiety disorders, the lifetime prevalence of panic disorder, obsessive-compulsive disorder and generalized anxiety disorder were shown to be three times as common among MS patients than among the general population, while social anxiety was less common[124]. A problem might be that anxiety in itself - in contrast to the anxiety disorder diagnoses - is not well defined as a diagnosis, nor well characterized as a symptom, in the psychiatric literature[24].

Sleeping problems are among the most commonly reported symptoms in MS patients, with insomnia having been reported among more than 50%[125]. Sleeping problems are associated with other common MS symptoms such as pain, restless legs and fatigue. Poor sleep quality is associated with fatigue, depression and anxiety[126].

Although less common, an elevated risk has been reported among MS patients also for bipolar disorder[53, 127]. An association with psychotic disorders has been demonstrated in some studies [128] but not in others[53]. Changes in personality traits have been reported in MS suggesting a frontal affection[129]. An increasing body of research on personality traits have shown them to mediate the relation between gray matter volume and psychiatric symptoms[130], predict quality of life[131], and be related to occupational stress[132]. The concept of personality traits should, however, be distinguished from the current psychiatric diagnostic concept of personality disorders, the prevalence of which is unknown in MS patients.

In stages of advanced disease, MS patients have increasing rates of conditions with a more neuropsychiatric profile such as pseudobulbar affects (pathological laughing and crying)[133] and euphoria/apathy[134].

1.2.7 MS and stress

MS patients have been proposed to have alterations in the hypothalamic-pituitary-adrenal axis function, the most important stress-response system which is also associated with the innate immune response[135]. Stressful life events of various kinds have been associated with the appearance of new MR lesions[136] as well as with exacerbations[137]. Coping mechanisms were shown to moderate this association[138]. The question whether physical trauma is associated with the onset of multiple sclerosis has been controversial, but a qualitative review article excluded an association[139]. A recent meta-analysis, however, saw an association with MS onset for some types of premorbid trauma in case-control studies, but not in cohort studies[140]. MS patients have a higher risk than healthy controls for having experienced childhood trauma[141]. This was associated with number of relapses, but not with disability.

1.2.8 The relationship between depression, cognitive dysfunction and fatigue

Being in some ways overlapping, but phenomenologically distinct, the concepts of depression, cognitive dysfunction and fatigue seem to have a complex relationship in MS patients. This has given rise to a diverse and often conflicting body of literature trying to establish associations and/or causal connections between two or all three concepts.

Depression and fatigue have been showed to be highly correlated, even when somatic depressive symptoms were excluded[142,143]. Depressed patients have greater fatigue symptoms[118] and have notable symptom overlap[144]. Depression is also associated with worsening of fatigue symptoms over time[145]. Fatigue may be harder to treat when an untreated depression is present[144]. Causality, if it exists, is complex, as depression can predict later fatigue and anxiety, while anxiety and fatigue can predict later depression[146]. Psychological factors such as a sense of loss of control over one's environment could be a shared underlying component[147,148].

Early studies of cognitive dysfunction in MS patients did not reveal an association with depression[76, 149], but results were perhaps confounded by not controlling for vegetative symptoms such as fatigue[81]. Later studies quite consistently showed that depression affects information processing and working memory[150-152] as well as executive functions[151]. Non-somatic depressive symptoms was the strongest clinical predictor for cognitive impairment in one study, in which no association with fatigue was found[153]. This lack of association between cognitive dysfunction and fatigue is consistent with the findings of other studies[152,154,155]. However, recent findings include fatigue being associated with decreased attention and vigilance[156], although the overlap with depressive symptoms may not have been considered[157].

1.2.9 Comparisons of prevalence with other medical conditions

MS is a unique disease regarding the combination of its mechanism of inflammation in the CNS, onset in young adult life, and chronic and fluctuating course, creating a special profile regarding the risk for psychiatric comorbidity which is not wholly comparable to other

medical conditions. Furthermore, in order to make adequate comparisons regarding prevalence of comorbidities, the same methods should be used in when comparing the diseases which preferably means studying them simultaneously, which is rare. However, some comparisons can be made.

Rheumatoid arthritis (RA) is a chronic, often disabling inflammatory disease with increasing incidence with age, peaking between ages 40 and 50[158]. It is more common among women[158]. As with MS, several new treatments have emerged in the last decade, but in the case of RA, these treatments have improved outcomes dramatically for many patients[159]. Depression is the most common comorbidity in RA, with a prevalence of more than 15% in meta-analyses[160] and 37% using the PHQ-9[161]. Depression is associated with disability[161] and lower age[160]. Although much less studied, anxiety was more common than among controls and more common than depression in one population-based study on chronic arthritis[162]. Suicide risk has not been determined among RA patients, but the risk for suicide attempts is increased[163].

Systemic lupus erythematosus (SLE) is, like MS, a chronic autoimmune disorder, which can among other organs affect the CNS. It commonly has a relapsing-remitting course. It is also more common among women, and the most common age of onset is young middle age[164]. In a systematic review[165], depression prevalence ranged between 17-75%, with MDD diagnosis at 20-47%. However, no register studies were included and the maximum number of participants in any study was 326. In most studies, depression was not related to symptom severity. The most common neuropsychiatric comorbidity in SLE is perhaps cognitive dysfunction[166]. In a direct comparison, a selection of MS patients tested more poorly on several cognitive domains than SLE patients, while depression scores were similar[167]. Cognitive symptoms were negatively associated with vocational status in both groups. Anxiety may afflict up 24% of SLE patients[168]. No estimations of risk for attempted or completed suicide risk exist. Suicide ideation was associated with higher symptom burden and unemployment[169]. Unlike MS or RA, the literature on SLE generally uses the term "neuropsychiatric symptoms" inherent to the disease rather than "comorbidity".

1.3 CYTOKINES IN MS AND PSYCHIATRIC DISORDERS

1.3.1 Cytokines in MS

Cytokines are small proteins vital for cell signaling, especially in the immune response. They can be produced by several cell types and act via receptors on receiving cells. Normal cytokine levels are low or absent[170]. They are typically produced in small quantities as a response to the environment or to signaling, for example through other cytokines. A balance is maintained by pro- and anti-inflammatory cytokines[171].

Cytokines have been implicated in the pathogenesis of MS in several ways[172]. MS patients have been treated with interferon-beta (IFN-β) for over twenty years[173], and it is today the

first-line treatment of RRMS. On the other hand, treatment with IFN-ϒ can induce exacerbations[174]. Only activated T-cells can cross the blood-brain barrier[175]. Activated T-helper (Th) cells produce several cytokines; Interleukin(IL)-12, IFN-ϒ and Tumor necrosis factor (TNF)-α which induce Th1-type immune (pro-inflammatory) responses, while IL-6 and IL-10 induce Th2-type (mostly anti-inflammatory) responses. There seems to be an imbalance in favor of Th1-mediated cell response in MS, further supporting the notion that the disease is an autoimmune one[176]. TNF-α, IFN-ϒ and IL-10 are present in active brain lesions[177]. Transgenic animal studies indicate that overexpression of IL-6, IFN- ϒ and TNF- α by astrocytes induces demyelination[178]. The interest in cytokines as MS-specific biomarkers has waned in later years due to their very general role in the immune response of a number of pathological conditions, with the possible exception of CXCL13 in the cerebrospinal fluid (CSF)[179]. However, the central position of the IL-6 family in regulating the immune response in MS, inducing an anti-inflammatory phenotype in macrophages[180] and stimulating Th17-cell differentiation[181], has suggested that blocking the IL-6 pathway may limit immune-mediated tissue injury[182].

Unfortunately, cytokine detection in MS blood or CSF samples varies widely between studies[176,183-185]. Most studies have focused on the theoretically most important cytokines mentioned above, with varying results. MS patients have been shown to have elevated concentrations of both pro- and anti-inflammatory cytokines in blood compared to healthy subjects, independent of disease sub-type[186]. However, levels of most of these cytokines do not differ in CSF compared to non-MS controls[185] and detection levels of many cytokines in CSF are low.

1.3.2   Cytokines in MS depression, stress, cognitive dysfunction and fatigue

Outside of the MS field, cytokines has long been of interest in the search for biomarkers for depression. Cytokines can induce "sickness behavior", i.e. behavioral changes that correspond to a physiological adaption to inflammation, but in susceptible individuals this has been hypothesized to develop into depression[187].

There is evidence in depressed patients of upregulation of IL-1, IL-2, IL-6 and TNF-α in plasma[188,189]. Therapeutical administration of IFN-α, e.g. for hepatitis A, can cause depression and anhedonia[190]. Moreover, the depression severity correlates with higher CSF levels of IL-6 and lower levels of the serotonin (5-HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA)[191], as well as increased L-kynurenine (KYN)[192]. Cytokines, in particular IFN-γ, can increase the enzyme indoleamine-2,3-dioxygenase (IDO)[193], shifting the precursor amino acid tryptophan away from the 5-HT-synthesizing indolamine pathway to the alternate KYN pathway. In two meta-analyses including serum, plasma and CSF samples, TNF-α and IL-6 were elevated in depressed subjects compared with control subjects[194,195], and also soluble IL-2 receptors[196]. It is unclear whether this inflammation precedes, or is caused, by depression[197]. Inflammatory cytokines is also linked to suicidal behavior[198]. Patients who had increased serum levels of TNF-α and

responded to antidepressant medication had lowered levels after treatment, which was not the case for non-responders[199].

Being a neuroinflammatory condition with high rates of depression, MS has been suggested as an ideal model to study immune-mediated mood disorders[200]. Looking specifically at cytokine studies on MS and depression, TNF- α and IFN- ϒ mRNA expression in peripheral blood correlates with symptom severity in depressed patients[201]. MS patients who responded to antidepressive treatment had significantly lowered levels of serum IFN-γ after treatment[202]. Further support for the role of cytokines comes from animal studies. Experimental autoimmune encephalomyelitis (EAE) is the most common model of MS. In EAE animals there are correlates of depressive behavior even before onset of demyelination. This behavior is associated with elevated IL-1β and TNF-α in the hypothalamus and changes in the hypothalamic-pituitary-adrenal (HPA) axis[203]. Inflammation did also modulate anxiety in EAE mice, which correlated with increased TNF-α levels in the hippocampus[204].

Regarding MS fatigue, evidence of association with cytokines is inconsistent. While some studies fail to establish a correlation[205], others have shown correlation of fatigue scores with IFN- ϒ and TNF-α[206], and blood TNF-α mRNA[207].

Tying depression and fatigue together, patients with MS and depression have been shown to have increased levels of cytokine-producing CD8+ T-cells – but this finding was even stronger correlated to fatigue[208]. Also, when comparing fatigued to non-fatigued patients, stimulated production of IFN-γ by peripheral CD3+CD4+ T lymphocytes was related to both fatigue and co-morbid depression[209].

The topic of cytokines in relation to cognitive dysfunction has been, in comparison, little studied. When comparing cognitively impaired with cognitively preserved MS patients, the rate of IFN-γ-positive CD4+ and CD8+ T-cells showed modest correlation with processing speed and working memory but was, unexpectedly, significantly higher among preserved patients[210]. Cytokines such as IL-1β, IL-6 and TNF-α have been suggested to play an important role in physiological cognitive processes[211].

1.4   MS AND WORK DISABILITY

Although the clinical course and symptoms of MS can vary widely, the disease often causes severe disability which can affect many aspects of a patient's life, such as employment status. Over 60% of MS patients of working ages are on disability pension (DP)[212]. Patients often enter DP only a few years after diagnosis, in the third and fourth decade of life. RRMS patients have higher employment rate than patients with progressive disease[213]. Of patients still in employment, 34% have long-term sick leaves yearly[212]. Reduced working ability is associated with fatigue and neurological disability, as well as with lower education level[214], but cognitive dysfunction and fatigue may mediate the effect of disability on employment status[215].

MS patients have 15% lower earnings than matched controls, and patients with a sickness duration of at least five years have 38% lower earnings[216]. Figures for social benefits were 33% and 130% higher for MS patients. While the general populations' income gradually increase over life, MS patients' income decline[217]. Fifteen percent of patients report unmet needs regarding employment from the community[218].

The risk of being granted DP is doubled if the MS patient suffers a psychiatric co-morbidity[219]. In one cross-sectional study, mild depression among patients with benign MS was associated with a much higher risk of not being employed[220]. Better self-reported memory functioning and less social fatigue has been associated with increased working hours[221].

In Sweden, all adults below the age of 65 with a disease or injury that has led to permanent work incapacity can be granted DP[222]. DP, which may be granted for part- or full-time of ordinary working hours, covers up to 64% of the lost income up to a limit. Those with no previous income get a minimum level. The customary age for old-age pension is 65 years, but may be granted from the age of 61 years. The purpose of DP in the Swedish social insurance system is to alleviate the mental and physical strain of having to fulfill ordinary work duties in order to secure an income[222], but the actual consequences of receiving DP on MS patients' mental and physical health is largely unknown. Being outside the labor market for any reason has a negative association with MS patients' quality of life[223,224].

In the general population, study results are conflicting regarding the association of DP on mental health[225-227], perhaps due to differences in study methodology. However, when systematically reviewed, prospective studies which follow the subjects before, during, and after retirement and/or DP rather uniformly suggest better mental health after retirement[228].

Register studies on the general population have shown increasing rates of psychiatric prescriptions in the years leading up to DP pension, and decreasing rates afterwards[229-231]. When somatic and psychiatric DP diagnoses were looked at separately, patients with psychiatric diagnoses, and especially depression, had a steep increase in antidepressant prescriptions before DP, and corresponding large decrease after being granted DP. For somatic diagnoses, there was a slight increase of antidepressants in the years leading up to DP, and more of a plateau-shape after[230, 231].

2 AIMS AND OBJECTIVES

The overall aim of this thesis was to study the comorbidity of psychiatric symptoms and disorders in patients with MS, from both a clinical/biological and an epidemiological point of view. The study objectives ranged from examining prevalence of psychiatric comorbidity to studying its potential consequences – namely DP, suicide attempts, and suicide - as well as studying the relationship between stressful events or depression with immune markers in MS patients.

The specific objectives of the studies that compose this thesis were:

Study 1. To a) study the risk for having psychiatric diagnoses and being prescribed psychiatric medications in a nationwide cohort of MS patients compared to non-MS patients, and b) study whether psychiatric diagnoses and/or prescriptions were associated with the risk for future DP among MS patients.

Study 2. To study whether the number of years before or after being granted DP was associated with being prescribed psychiatric drugs in a sample of MS patients, and to compare this with a sample of matched non-MS control subjects who had also been granted DP.

Study 3. To study the risk and risk factors for attempted suicide and completed suicide in a nationwide cohort of MS patients, compared to a matched non-MS cohort.

Study 4. To study the relationship between depression, exposure to violence in childhood and adult life, and the cytokines IL-6 and IL-8 in CSF in a clinical cohort of MS patients.

3 METHODS

3.1 STUDY SUBJECTS

3.1.1 Study I and II

For these two studies, the study population was identified through a combination of data from five nationwide registers:

1. The National Patient Register (NPR), held by the Swedish National Board of Health and Welfare (NBHW), starting in the 1960s, with complete information on all in-patient care since 1987 and on specialized out-patient care since 2001. Variables registered include gender, age, place of residence, county council, hospital/clinic and department; as well as main and secondary diagnosis, external cause of injury and poisoning, and procedures, according to the version of the International Statistical Classification of Diseases and Related Health Problems (ICD) currently in use. The NPR has a high completeness, with missing data for main diagnosis at around one percent, and for external causes at three percent[232].

2. The Swedish Prescribed Drug Register, which provides information on all prescribed drugs, including dosage and Anatomical Therapeutic Chemical (ATC) code[233] dispensed at pharmacies in Sweden starting from July 2005[234]. This register is also held by the NBHW.

3. The Swedish Cause of Death Register, which comprises complete data since 1961 on date and cause of death, coded according to the current version of the ICD, for all deaths in Sweden among inhabitants registered in Sweden[235]. This register is also held by the NBHW.

4. The Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA)[236], a population-based register held by the government agency Statistics Sweden and updated annually since 1990. LISA contains various sociodemographic variables including source and size of income, occupational status, place of residence, country of birth and latest year of immigration.

5. The Micro Data for Analysis of the Social Insurance (MiDAS) database[237] held by the national Social Insurance Agency. This register contains data on diagnosis-specific DP and sick leave since 1994, including dates and grade (part or full time).

The subjects' unique personal identity numbers assigned to all Swedish residents were used to link data from different nationwide Swedish registers. All individuals who were 17-64 years old, and lived in Sweden, in 2005 were selected from LISA. Presence of MS was defined as being hospitalized or receiving specialized care at least once between 2000 and 2005 with a primary or secondary ICD-10 [238] diagnosis code G35 in the NPR. Thus, 10,791 MS patients and 5,628,982 non-MS individuals were identified.

In **study I** 65,091 individuals (of which 41 were MS patients) with missing values on place of birth and/or educational level at baseline were excluded which granted a cohort consisting of 10,750 MS-patients, identified through nationwide registers, and 5,553,141 non-MS individuals. For the second analysis in this study, only the 4,571 MS patients not on any DP in 2005 according to MiDAS were included.

In **study II** those MS patients were selected who were granted full-time DP, regardless of which diagnosis was stated as the main DP reason, in the years 2000-2012 (n=3,836). For every MS patient five matched control subjects were selected according to the procedure described under "Analysis". A flow chart for subject selection is shown in **Figure 1.**
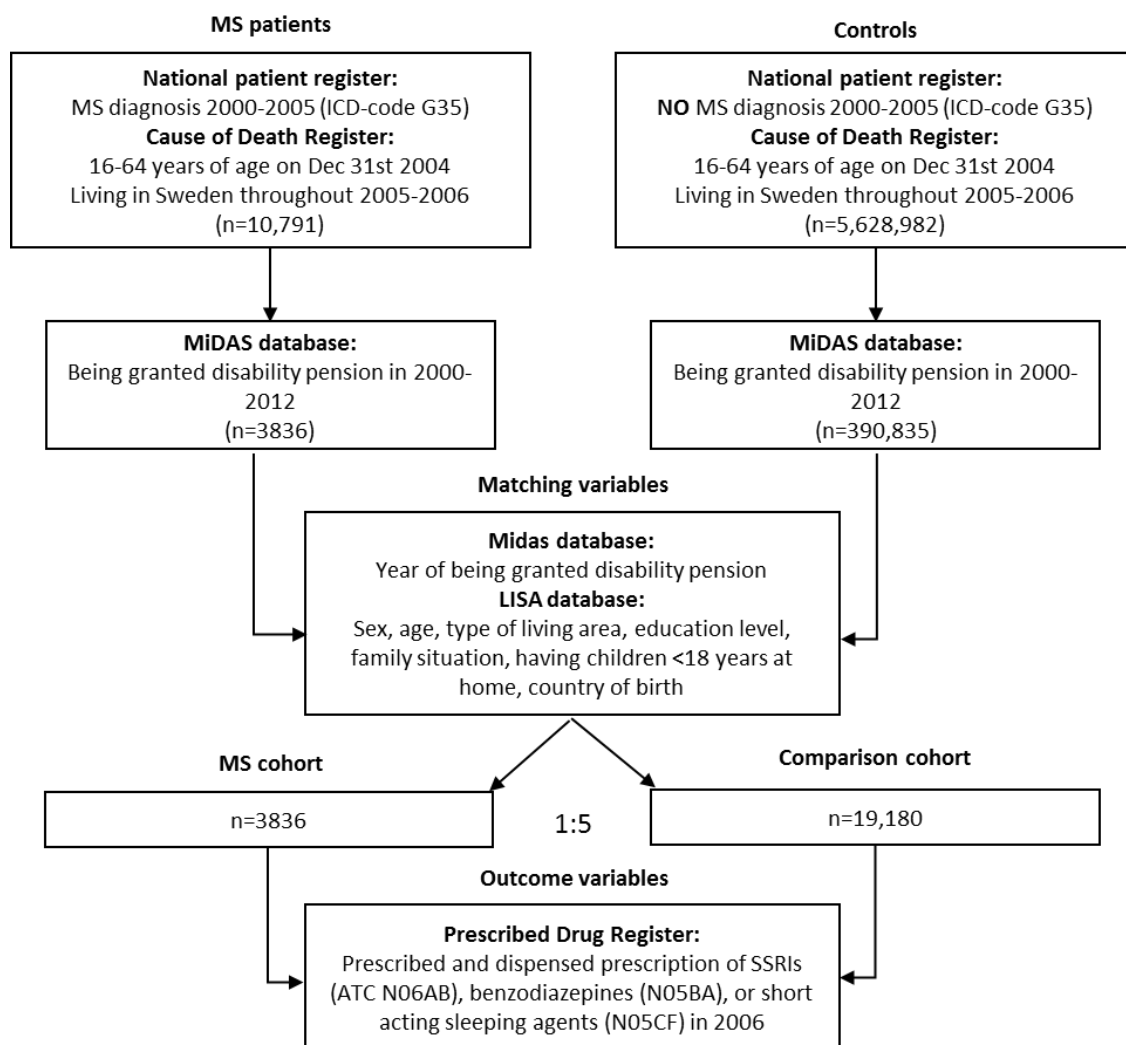

Figure 1: Study II. Variables from Swedish registers used for identifying subjects and analysis variables.

3.1.2   Study III

A total of 29,617 MS patients were identified through the NPR and the Swedish MS Register (SMSreg)[201] between 1968 and 2012. The SMSreg contains data recorded since 1996 for patients who provided written consent with a current nationwide completeness of

approximately 80%[201]. Diagnostic accuracy for MS in this register exceeds 95 percent[239].

Each MS patient was individually matched with ten Swedish residents without MS diagnosis by gender, year of birth and county of residence in Sweden at time for MS diagnosis (n=296,164). Matching was performed by the government agency Statistics Sweden. Members of the comparison cohort were selected at random from individuals who were alive at the time of MS diagnosis in the matched patients. For two of the MS patients only six and eight matched controls were available.

3.1.3   Study IV

During the study recruiting period of May 2012 to June 2014, all consecutive RRMS patients at the MS outpatient clinic at the Karolinska University Hospital, Solna who met the following criteria were asked to participate in the study: 1. A recent CSF examination from clinical practice, allowing for an interview session within 90 days of sampling. 2. Being 18-55 years of age. 3. Recent (≤2 years) MS diagnosis, or a current switch in drug treatment regime due to relapse and/or side effects. 4. No known main somatic or psychiatric diagnosis besides MS. 5. No current psychiatric or psychotropic medication, including glucocorticoids. The MS clinic serves an uptake area that includes the central-northern part of Stockholm County corresponding to about 40% of the entire population.

In total, forty-seven subjects who met the criteria and gave informed consent were included in the study. A flow chart for subject selection is shown in **Figure 2.**
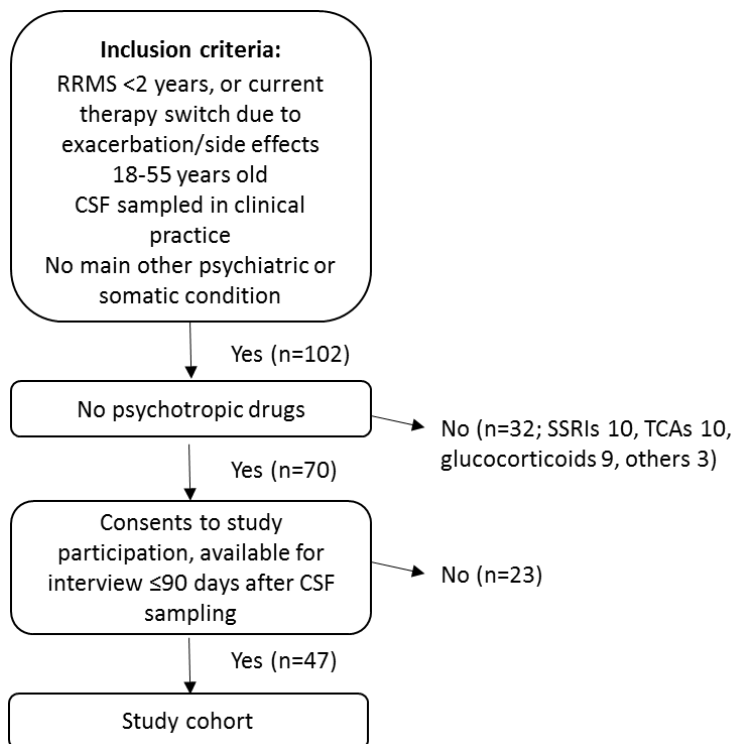

Figure 2. Study IV. Study recruitment flow chart. RRMS = Relapsing remitting multiple sclerosis, CSF = cerebrospinal fluid, SSRIs = Selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

3.2 OUTCOME VARIABLES AND COVARIATES

3.2.1 Study I and II

Information for 2005 was obtained from LISA regarding age-groups (17-34, 35-44, 45-54, 55-64), sex, educational level (compulsory school (≤9 years), high school (10-12 years), university (≥13 years), country of birth (Sweden, the other Nordic countries, other EU 25, all other countries), and type of living area (based on the H-region classification scheme [240] and divided into the following three categories: larger cities (H1-H2), medium-sized (H3-H4) municipalities or smaller municipalities (H5-H6)).

For **study I**, psychiatric comorbidity was identified using the ICD-10 codes F00-F99, here organized into nine categories: developmental and organic disorders (F00-09, F70-F89), disorders related to substance use (F10–F19), schizophrenia and non-affective psychoses (F20-29), bipolar disorder (F31), depressive disorders (F32-F33), affective disorders (F30-39, including bipolar disorder and depressive disorder), neurotic and somatoform disorders (F40-F42, F44-F49), stress-related mental disorders (F43), behavioral disorders (F50–F59, F90–99), and personality disorders (F60–F69).

Psychiatric medication was defined as a dispensed prescription for a drug with the ATC codes N03-N07 at least once between July and December 2005. The codes were organized into nine different groups according to pharmacological class and/or clinical use: selective serotonin reuptake inhibitors (SSRIs; N06AB), tricyclic antidepressants (TCAs; N06AA), other antidepressants (N06AG02, N06AX), first generation antipsychotics (FGA; N05AA-N05AD, N05AF), second and third generation antipsychotics (SGA); N05AE, N05AH0, N05AX), benzodiazepines (N03AE01, N05BA, N05CD), short-acting sleeping agents (N05CF), lithium (N05AN01), and alcohol dependence drugs (N07BB). Anti-convulsants and central stimulants were considered but not included as their use in MS patients is primarily for non-psychiatric indications.

In **study II** the Swedish Prescribed Drug Register was used to obtain information on the number of MS patients and non-MS controls with at least one dispensed prescription of SSRIs, benzodiazepines, or short acting sleeping agents in 2006.

3.2.2 Study III

Attempted suicide was defined as being treated as a hospital inpatient or outpatient for some form of self-harm that had been recorded as attempted suicide using ICD diagnostic and accident codes (ICD-8 and -9 950-959, ICD-10 X60-X84).

Suicide as the cause of death was identified through the Cause of Death Register. Completed suicide was defined as the same ICD codes as for attempted suicide stated as main or contributory cause of death. Deaths with undetermined intent were not included as this could possibly overestimate actual rates[241].

A measure of educational level was constructed from census data from Statistics Sweden (from 1960 onwards), with categories for compulsory school or less, upper secondary, higher education, and no educational data available, using the highest recorded level. Dates of death and emigration for the entire study period were obtained using the Total Population Register[242], which is held by the Swedish Tax Agency and contains current data on residents in Sweden regarding such variables as place of residence, family ties, and date and place of births and deaths. Linkage between data sources was possible using the subjects' personal identity numbers.

3.2.3 Study IV

During a single session, participants were subject to two semi-structured clinical interviews conducted by a trained psychiatrist. The MINI International Neuropsychiatric Interview (M.I.N.I.) version 6.0.0.b[243], uses DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition)[244] criteria to screen for and clinically validate psychiatric diagnoses, including MDD. The Karolinska Interpersonal Violence Scale (KIVS) [245] includes four subscales, each ranging from 0-5, measuring exposure to/used interpersonal violence as a child (6–14 years old) or adult (15 years of age or older). Violence exposure ranges from occasional, low-grade violence (1) up to repeated, serious battering or harm (5). The KIVS has a good interrater reliability[245].

The subjects also filled out the Montgomery-Åsberg Depression Rating Scale, self-report version (MADRS-S)[246], which is a nine item questionnaire for rating of depressive symptoms according to the DSM criteria for MDD. In order not to confound depressive symptoms with common MS-related symptoms such as fatigue or sleeping problems, the five cognitive items in the MADRS-S scale (covering the symptoms depressed mood, anxiety, pessimism, loss of interest and suicidality) were separated for analysis. Disability was rated at the time of CSF sampling with the Expanded Disability Status Scale (EDSS)[101].

Foror the laboratory analysis, CSF samples were collected through lumbar puncture using Sprotte® spinal needles. The CSF was collected in plastic tubes and centrifuged at 2442 rcf for 10 minutes. The supernatant was aliquoted and frozen at -70 ℃ within three hours of sampling.

Cytokines IL-6 and IL-8 were analyzed from previously unthawed CSF supernatants using ELISA kits from R&D systems® (Quantikine® ELISA; MN, USA) according to the manufacturer's protocol. Briefly, standards were reconstituted and serially diluted. Undiluted CSF samples, standards and negative controls were added to 96 well pre coated plates in duplicates after prior addition of assay diluent in equal quantity to all wells. After incubation, wells were thrice rinsed with wash buffer, decanted and blotted against clean paper towels. Interleukin conjugates were added, plates were covered with adhesive strips and left to incubate. The wash step was repeated as described above. Substrate solution was added and plates were kept protected from light at room temperature for color development, which was then abrogated by adding stop solution. Plates were read using a microplate reader

(Spectramax® plus 384, Molecular devices, CA, USA) set to 450 nm. Results were acquired and analyzed using SoftMax Pro (version 6.2.1, Molecular devices, CA, USA).

3.3 STATISTICAL ANALYSIS

3.3.1 Study I

First, descriptive analyses were performed to explore the distribution of the baseline covariates among MS patients and non-MS individuals, respectively. Second, logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for the outcomes psychiatric in- and out-patient care (2001-2005) and psychiatric drug prescriptions (July-December 2005), for MS-patients compared to non-MS individuals. The analyses were adjusted for age group, sex, educational level, country of birth, and type of living area.

Third, among the 4,571 MS patients not on DP in 2005, survival analyses were performed with psychiatric diagnoses and medication as exposures, and disability pension as the outcome. The cohort members were followed from 2006 through 2010, or the year the individual turned 65, emigrated, died, or was granted old age pension or DP, whichever occurred first. In each analysis, the reference group included all subjects without the exposure tested (i.e. included subjects with all other diagnosis groups and/or medications). Hazard ratios (HR) with 95% confidence intervals (CI) were estimated by proportional hazards models. The analyses were adjusted for age group, sex, educational level, country of birth, and type of living area. The assumption of proportional hazards was tested and met using log/(-log) plots. Each diagnosis group and prescribed drug class was analyzed separately throughout the study, not taking into account any co-occurrence of other diagnoses or drugs in the subjects.

Fourth, two-way interactions between age/sex and the exposure variable were introduced in both regression and survival models to evaluate the fit of the models. These interactions were either deemed non-significant, or did only affect the results marginally. Correction for multiple comparisons was performed using the Holm-Bonferroni method[247].

3.3.2 Study II

Patients and controls were matched by year of DP and then by socio-demographic variables from the LISA database for 2005; sex, age, type of living area, education level, family situation, having children <18 years at home, and country of birth. Variables were organized into categories for sex, age group (17–34, 35–44, 45–54, 55–65 years), educational level (lower education <12 years or higher education ≥12 years), country of birth (Sweden or other country), family situation (married/cohabitant or single), having children <18 years living at home (yes/no), and type of living area (large, medium or smaller municipalities according to the H classification). A possible MS diagnosis after 2006 was not an exclusion criteria for being selected as a control subject.

Propensity scores were generated in a logistic regression analysis with MS (yes/no) as the dependent variable, and socio-demographic variables (sex, age, type of living area, education level, family situation, having children <18 years at home, and country of birth) as covariates. The model was evaluated with a Hosmer-Lemeshow test with p>0.05. An 8 to 1 digit Greedy matching algorithm was performed to match MS patients with non-MS controls. Covariate balance was assessed by the standardized difference method for categorical variables[248]. An absolute standardized difference below 10% indicates that no meaningful covariance imbalance was present[249], and after matching the values ranged between 0-1.5%.

In order to perform a cross-sectional study with 2006 being the study year (the year data on prescribed dispensed psychiatric drugs was measured), the MS patients and non-MS controls were categorized by year of full-time DP into seven study groups: 2000-01, 2002-03, 2004-05, 2006, 2007-08, 2009-10, and 2011-12, respectively.

After control matching, descriptive analyses were performed to explore the distribution of the socio-demographic covariates among the MS patients. Second, adjusted odds ratios (OR) with 95% confidence intervals (CI), were calculated for MS patients and non-MS controls (in separate analyses) with those being granted DP in 2006 as the reference group, to determine risk for being prescribed the three classes of psychiatric drugs in 2006. The study groups were analyzed separately among both MS patients and controls. The three drug classes were analyzed separately, without taking into account any co-occurrence of other drugs.

Third, adjusted OR with 95% CIs were calculated for MS patients compared to non-MS controls regarding risk for prescription of the respective psychiatric drugs using General Estimating Equations (GEEs) with an exchangeable correlation matrix[250]. GEEs were performed due to clustering introduced by the matching procedure, allowing comparison of MS patients and controls within each of the seven study groups. Two-way interactions between covariates and the exposure variable were introduced in all analyses to evaluate the fit of the models, all of which were statistically non-significant (p>0.05).

3.3.3 Study III

Separate Cox regression analyses were performed for attempted and completed suicide with attained age as the underlying time scale. The reference group was the unexposed (non-MS) group. Subjects were followed from first recorded MS diagnosis (and the same time-point for matched comparators) and ending at attempted suicide or completed suicide, emigration, death, or study end in 2012, whichever occurred first. HR with 95% confidence intervals CI were estimated for crude analyses, and also adjusted for sex, residential place at entry, year of entry and highest attained education level. Analyses were also stratified by sex, education, year of study entry, and duration after study entry. Separate analyses for MS and non-MS cohorts were also performed using a dichotomous variable for education (≤14 years versus >14 years). Interaction between MS and sex was tested and found non-significant.

In the analysis for attempted suicide 453 MS patients and 3,557 non-MS comparators were excluded because of attempted suicide before entry. Among non-MS comparators, 4,456

subjects were also excluded as they were matched to a subject with MS who was excluded due to attempted suicide before entry. A sensitivity analysis was performed in which subjects who attempted suicide before entry were not excluded from the analysis and included in an adjusted model. The proportional hazards assumption was tested and met for all strata.

3.3.4 Study IV

First, unadjusted as well as partial (adjusted for sex and age) two-tailed nonparametric correlation analyses were performed on IL-6 and IL-8, respectively, and age, EDSS score, the MADRS-S cognitive score, MADRS-S total score, the KIVS exposure to violence as a child score, and the KIVS exposure to violence as an adult score. Median values for IL-6 and IL-8 were compared between men and women, and between subjects with and without MDD diagnosis, using non-parametric tests.

Second, multiple regression analyses were performed with IL-6 and IL-8, respectively, as dependent variables, with age, sex, MDD diagnosis, EDSS score, and the KIVS score for exposure to violence as a child *or* the KIVS score for exposure to violence as an adult, as independent variables. Three patients had IL-6 values under the detection level; these were replaced with values 50% below the lowest values in the sample. Non-normal variables were transformed through square root transformation, or, if this did not yield a normal distribution, Blom transformation[175]. Interaction variables for sex vs. exposure to violence and depression were sequentially tested and excluded from the models. The fit of the models was confirmed through plotting of residuals. In an additional analysis, MDD diagnosis was replaced by the cognitive score from the MADRS-S. Potential mediation effects in the models were explored with the PROCESS procedure[251] in SPSS (v23.0, IBM Corp.), which was the program used for all statistical analyses. For sensitivity, all regressions which included MADRS-S cognitive score were rerun with the total MADRS-S score for comparison.

4 RESULTS

4.1 STUDY I

Compared to non-MS subjects in this study, the MS patients were generally older, with a mean age of 47 vs 41 years, and more often female, 71% vs 49%. DP was clearly more common among MS patients, 61% compared to 10% among non-MS subjects. A larger proportion of MS patients were born in Sweden, 91% compared to 86%. Other socio-demographic data did not differ substantially.

In **Table 1,** numbers and percentages of individuals with a psychiatric diagnosis or medication are shown for MS patients and non-MS subjects, respectively. It also shows the results of the logistic regression analysis presented as adjusted ORs. Ten percent of MS patients had received a psychiatric diagnosis, compared to 5.7% of non-MS individuals (OR 1.82 (95% CI 1.71-1.94)). Depressive disorder was the most common diagnosis in both groups; 4.4% of MS patients and 1.7% of the non-MS individuals, respectively (OR 2.41 (95% CI 2.22-2.64)). All psychiatric diagnoses were overrepresented among MS patients, except for personality disorders and substance abuse for which rates were approximately equal.

Thirty-five percent of MS patients had been prescribed a psychiatric drug compared to ten percent of non-MS subjects (OR 3.72 (95% CI 3.57-3.88)). Twenty-five percent of the MS patients had been prescribed an antidepressant, most commonly SSRIs (17%), compared to 6.5% of the non-MS individuals, (OR 3.64 (95% CI 3.48-3.80)). Eleven percent of the MS patients had been prescribed benzodiazepines and 13 percent sleeping agents, while the proportions among the non-MS individuals where three and four percent, respectively (ORs 3.39 (95% CI 3.19- 3.61) and 2.70 (95% CI 2.55-2.86)). Medication for alcohol dependence was the only drug group less prescribed to MS patients (OR 0.59 (95% CI 0.35-1.00)).

Table 1. Study I. Psychiatric diagnoses and medications in multiple sclerosis (MS) patients and non-MS individuals; absolute numbers, percentages and adjusted odds ratios (ORs) with 95% confidence intervals (CI)

	MS (n=10,750)		Non-MS (n=5,553,141)			
Diagnoses	**n**	**(%)**	**n**	**(%)**	**OR***[a]*	**(95%CI)***[a]*
Developmental, organic disorders	148	(1.4)	17,778	(0.3)	4.66	(3.96-5.49)*
Substance abuse	162	(1.5)	99,474	(1.8)	0.94	(0.81-1.10)
Psychotic disorders	82	(0.8)	31,728	(0.6)	1.25	(1.01-1.56)
Depressive disorders	471	(4.4)	95,275	(1.7)	2.41	(2.22-2.64)*
Bipolar disorder	51	(0.5)	12,072	(0.2)	1.73	(1.31-2.27)*
Affective disorders	542	(5.0)	109,969	(2.0)	2.37	(2.18-2.59)*
Neurotic, somatoform disorders	303	(2.8)	88,768	(1.6)	1.67	(1.49-1.88)*
Stress-related disorder	170	(1.6)	52,244	(0.9)	1.65	(1.42-1.92)*
Behavioral disorders	85	(0.8)	32,492	(0.6)	1.68	(1.36-2.08)*
Personality disorders	42	(0.4)	22,088	(0.4)	0.98	(0.72-1.33)
Any psychiatric diagnosis	1074	(10.0)	317,493	(5.7)	1.82	(1.71-1.94)*
Prescribed dispensed medication						
SSRIs	1793	(16.7)	252,027	(4.5)	3.24	(3.08-3,41)*
TCAs	591	(5.5)	48,405	(0.9)	4.59	(4.22-5.00)*
Other antidepressants	575	(5.3)	95,879	(1.7)	2.55	(2.34-2.78)*
Any antidepressant	2685	(25.0)	363,592	(6.5)	3.64	(3.48-3.80)*
FGA	112	(1.0)	36,626	(0.7)	1.25	(1.04-1.51)
SGA	116	(1.1)	32,307	(0.6)	1.74	(1.45-2.09)*
Any antipsychotic	214	(2.0)	62,075	(1.0)	1.53	(1.33-1.75)*
Benzodiazepines	1134	(10.5)	139,490	(2.5)	3.39	(3.19-3.61)*
Sleeping agents	1324	(12.3)	199,339	(3.6)	2.70	(2.55-2.86)*
Lithium	38	(0.4)	11,383	(0.2)	1.29	(0.94-1.77)
Drugs for alcohol dependance	14	(0.1)	11,716	(0.2)	0.59	(0.35-1.00)
Any psychiatric drug	3801	(35.4)	558,725	(10.1)	3.72	(3.57-3.88)*

*[a]adjusted for age, sex, education level, country of birth, and type of living area, *= significant after Bonferroni-Holm correction for multiple comparisons. SSRI=Selective Serotonin Reuptake Inhibitors, TCA=Tricyclic Antidepressants, FGA = First generation Antipsychotics, SGA = Second generation Antipsychotics*

The results from the survival analysis are shown in **Table 2**. MS patients with any psychiatric diagnosis had a higher HR for DP than MS patients without a diagnosis; HR 1.83 (95% CI 1.53-2.18). The diagnosis group with the highest HR for DP was personality disorders; HR 5.42 (95% CI 2.98-9.83). MS patients with a depressive disorder diagnosis had a doubled HR for DP, HR 1.95 (95% CI 1.54-2.47). HRs were elevated in all diagnostic groups except for bipolar disorder.

MS patients with a psychiatric drug prescription of any kind had a higher HR for DP, HR 2.09 (95% CI 1.84-2.33) than MS patients without a prescription. The drug group with the highest HR was antipsychotics, HR 2.56 (95% CI 1.48-4.44). Those prescribed SSRIs, the most common group, had a doubled HR for DP, HR 2.15 (95% CI 1.85-2.49). All separate drug groups were associated with an elevated risk for DP.

Table 2: Study I. The hazard ratio (HR) with 95% confidence intervals (CI) for being granted disability pension during a five-year follow up (2006-2010) in multiple sclerosis (MS) patients not on disability pension in 2005, n=4750.

Diagnoses	Events/patients (%)	Adjusted HR (95% CI)
Developmental, organic disorders	14/24 (0.5)	3.59 (2.11-6.11)*
Substance abuse	19/40 (0.9)	2.20 (1.39-3.47)*
Psychotic disorders	3/11 (0.2)	1.06 (0.34-3.29)
Depressive disorders	75/161 (3.6)	1.95 (1.54-2.47)*
Bipolar disorder	3/10 (0.2)	0.99 (0.32-3.10)
Affective disorders	77/172(3.8)	1.85 (1.47-2.33)*
Neurotic, somatoform disorders	46/113 (2.5)	1.72 (1.28-2.31)*
Stress-related disorders	30/63 (1.4)	2.03 (1.41-2.93)*
Behavioral disorders	9/30 (0.7)	1.23 (0.64-2.37)
Personality disorders	11/12 (0.3)	5.42 (2.98-9.83)*
Any psychiatric diagnosis	144/342 (7.6)	1.83 (1.53-2.18)*
Prescribed dispensed medication		
SSRIs	207/415 (9.2)	2.15 (1.85-2.49)*
TCAs	61/123 (2.7)	2.04 (1.58-2.63)*
Other antidepressants	74/155 (3.4)	2.02 (1.60-2.56)*
Any antidepressant	309/632 (14.0)	2.23 (1.96-2.54)*
FGA	8/15 (0.3)	2.48 (1.23-4.99)
SGA	6/13 (0.3)	2.37 (1.06-5.30)
Any antipsychotic	13/26 (0.6)	2.56 (1.48-4.44)*
Benzodiazepines	74/168 (3.7)	1.77 (1.40-2.24)*
Sleeping agents	138/320 (7.1)	1.73 (1.45-2.07)*
Lithium	3/9 (0.2)	1.11 (0.36-3.44)
Drugs for alcohol dependance	1/2 (0.0)	1.30 (0.89-1.89)
Any psychiatric drug	403/900 (19.9)	2.09 (1.84-2.33)*

[a]adjusted for age, sex, education level, country of birth and type of living area *= significant after Bonferroni-Holm correction for multiple comparisons. SSRI=Selective Serotonin Reuptake Inhibitors, TCA=Tricyclic Antidepressants, FGA = First generation Antipsychotics, SGA = Second generation Antipsychotics

4.2 STUDY II

In the descriptive analysis the expected socio-demographic differences between the study groups were found. The MS patients granted DP earlier were older, less often had children living at home, and had a lower educational level than MS patients granted DP later in the study period (i.e., 2011/12). The number of patients in each group declined with later years of DP, as some reached the age of 65 and were thus not eligible for DP, and partly due to the inclusion criteria of the study (i.e., patients with a known MS diagnosis before 2006). The by far most common DP diagnoses among non-MS controls were mental disorders (ICD-10 codes: F00-99, 35.9%) and musculoskeletal disorders (ICD-10 codes: M00-99, 29.2%).

In the logistic regression analyses (**Figure 3**), MS patients and controls who had not yet been granted DP had approximately similar or lower ORs for psychiatric drug prescription than individuals that recently had been granted DP (in 2006) within their respective populations (i.e., patients and controls). ORs for all types of psychiatric drugs were lowest among those that were to be granted DP in 5-6 years from the reference year 2006 (i.e., study group 2011/12).

However, among MS patients who in 2006 had been on DP for 1 year or more, the ORs for being prescribed benzodiazepines were substantially higher, especially for those on DP since 5-6 years (study group 2000/01) (OR 1.73; 95% CI 1.16-2.57). This was not the case among the non-MS controls, where ORs were roughly equal to the reference group.

Regarding SSRIs, the ORs were lower among the non-MS controls who had been granted DP 5-6 years earlier (OR 0.78; 95% CI 0.68-0.89), which was not the case for the corresponding MS patients. For SSRIs, as well as for sleeping agents, ORs did not differ substantially between MS patients on DP for several years compared to patients recently granted DP (i.e., in 2006).

In the GEE analyses (**Figure 4**), the risk for being prescribed SSRIs for MS patients, compared with non-MS controls, was not elevated among those not yet on DP, regardless of the number of years until DP. However, MS patients who had been on DP for 3-4 and 5-6 years, respectively, had higher risks for being prescribed SSRIs (for the 5-6 years group: OR 1.76; 95% CI 1.44-2.15) compared to non-MS controls. Regarding benzodiazepines, MS patients with 5-6 years until DP had a substantially lower risks than controls (OR 0.53; 95% CI 0.30-0.96), while the risks among those already on DP was roughly equal between patients and controls. There were no significant differences in the risks regarding sleeping agents between MS patients and non-MS controls.
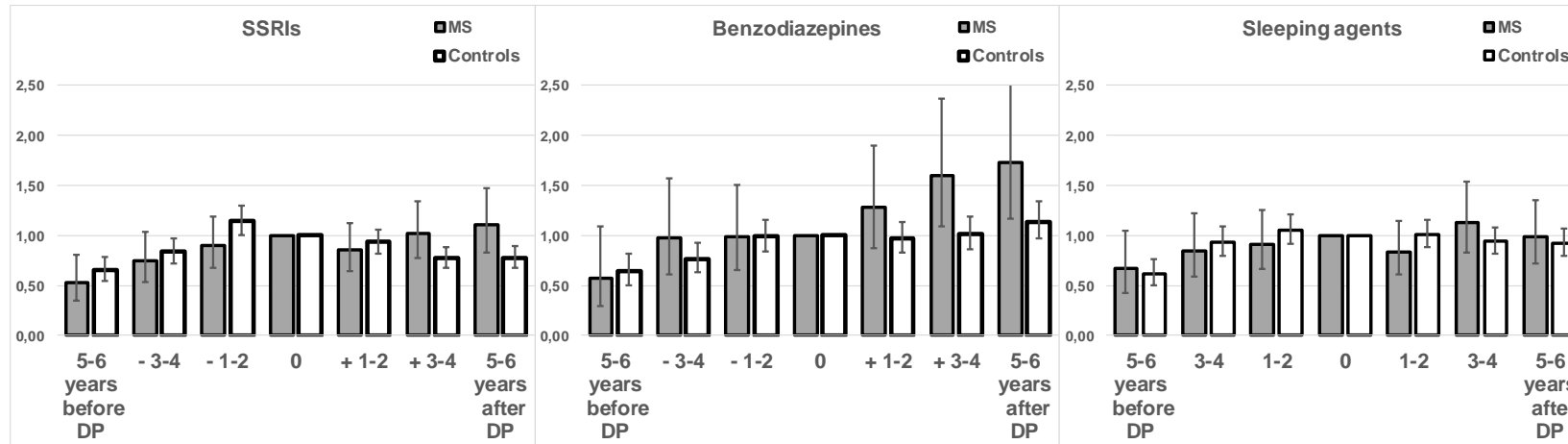
Figure 3. Study II. Risk for psychiatric drug prescription by year from disability pension. Odds ratios (OR) for MS patients and non-MS controls for being prescribed psychiatric drugs, by number of years before and after disability pension (DP) (=year 0). ORs are adjusted for sex, age, type of living area, education level, family situation, having children <18 years at home, and country of birth.
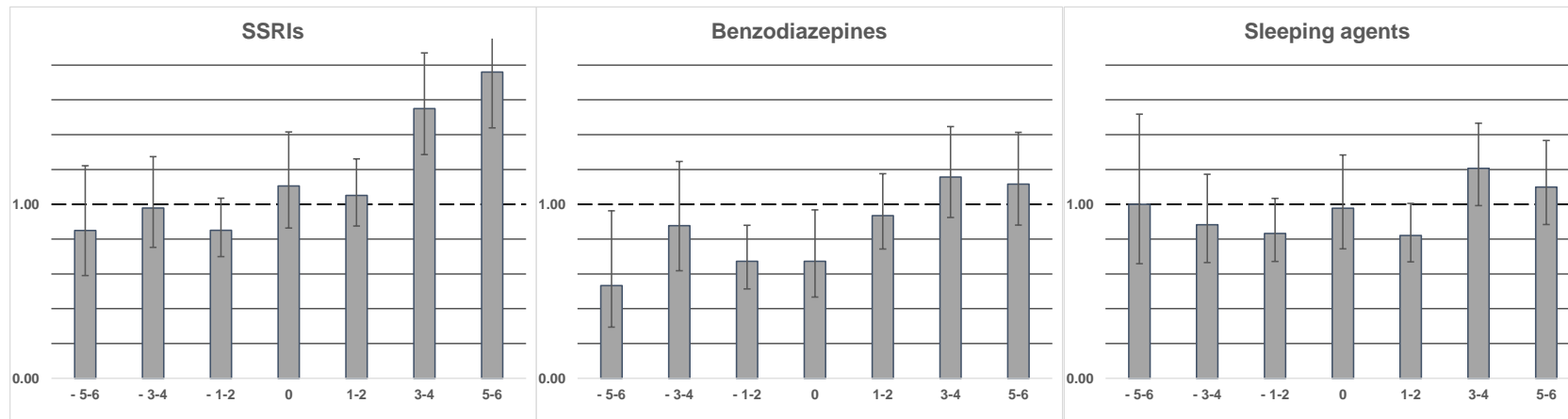

Figure 4. Study II. Risk for psychiatric drug prescription by year from disability pension – MS patients vs controls. Odds ratios (OR) for MS patients compared to non-MS controls for being prescribed psychiatric drugs - as the dependent variable in a General Estimating Equation analysis. Adjusted for sex, age, type of living area, family situation, having children <18 years at home, and country of birth. By number of years before and after disability pension (DP) (=year 0).

4.3   STUDY III

During follow-up, 423 individuals who attempted suicide and 114 who completed suicide were found among MS patients, with incidence rates (IR) of 116.5 and 30.31 per 100,000 person years. The corresponding IR among the non-MS cohort were 50.8 and 16.68.

Mean age and standard deviation for attempted suicide was 46.3 (±0.60) years among MS patients, and 49.6 (±0.35) years for non-MS comparators. Mean age for completed suicide was 51.8 (±1.13) years among MS patients, and 56.7 (±0.55) years for non-MS comparators. Thirty-seven percent of the suicide attempts in the MS cohort occurred within three years after study entry, 57% within 5 years, and 87% within 15 years. Twenty-nine percent of the completed suicides in the MS cohort occurred within three years after study entry, 53% within 5 years, and 86% within 15 years. While 64% of non-MS comparators with completed suicide used a violent method (not self-poisoning), the corresponding proportion was less than 53% for MS patients.

In **Table 3**, results for the whole study population (MS and non-MS combined) are shown with and without adjustments for covariates. In the whole study population, women were at higher risk for attempted suicide compared to men, while men were at higher risk for completed suicide. Higher education was associated with a reduction in the risk of attempted suicide compared with those who participated in upper secondary education, and to a lesser extent, so was compulsory school or lower. Higher education was associated with a reduction in the risk of completed suicide compared with those who participated in upper secondary education, but not compulsory school or lower. Compared to the non-MS group, MS patients had a more than doubled risk for attempted suicide, and an 80% risk increase for completed suicide, after adjustment for covariates.

Table 4 shows associations of MS, with non-MS comparators as reference, stratified by covariates (e.g. in the stratum of women, women with MS are compared with women who do not have MS). Both male and female MS patients had a more than doubled adjusted risk for attempted suicide compared with the non-MS group. The adjusted risk for completed suicide was more than doubled for women with MS and about 70% increased for men with MS. MS was associated with an increased risk of both attempted and completed suicide across educational levels. The risk of attempted suicide associated with MS was elevated compared with non-MS comparators regardless of decade of study entry. Risk for completed suicide was elevated for all decades except for the 1990s, where HRs were not statistically significant.

Table 3. Study III. -Hazard ratios (HR) and 95% confidence intervals (CI) for attempted and completed suicide

	Attempted Suicide		Completed Suicide	
	Unadjusted HR (95% CI) [a]	Adjusted HR (95% CI) [b]	Unadjusted HR (95% CI) [a]	Adjusted HR (95% CI) [b]
Overall				
Non-MS	Reference	Reference	Reference	Reference
MS	2.09 (1.88-2.32)	2.14 (1.92-2.37)	1.76 (1.44-2.14)	1.85 (1.52-2.26)
Sex				
Men	Reference	Reference	Reference	Reference
Women	1.29 (1.19-1.41)	1.29 (1.19-1.40)	0.37 (0.32-0.42)	0.38 (0.33-0.43)
Year of entry				
1968-1980	Reference	Reference	Reference	Reference
1981-1990	0.89 (0.80-0.99)	0.87 (0.78-0.97)	0.66 (0.56-0.78)	0.67 (0.56-0.80)
1991-2000	0.97 (0.87-1.08)	0.83 (0.74-0.93)	0.53 (0.44-0.65)	0.54 (0.44-0.66)
2001-2012	0.67 (0.60-0.74)	0.56 (0.50-0.62)	0.28 (0.22-0.34)	0.27 (0.22-0.34)
Education				
Compulsory school or less	0.73 (0.67-0.80)	0.69 (0.63-0.76)	0.97 (0.84-1.14)	0.84 (0.72-0.98)
Upper secondary	Reference	Reference	Reference	Reference
Higher education	0.61 (0.55-0.68)	0.62 (0.55-0.69)	0.69 (0.56-0.84)	0.74 (0.60-0.91)
No educational data	0.23 (0.18-0.29)	0.19 (0.15-0.24)	0.69 (0.53-0.90)	0.45 (0.34-0.59)

[a] *The variable indication exposure status (MS, non-MS) added to all unadjusted models.* [b] *Adjusted for sex, year of entry, education and region of residence at entry*

Table 4. Study III. Hazard ratios (HR) and 95% confidence intervals (CI) for attempted and completed suicide, stratified by sex, year of entry and education. Reference category is non-MS group.

	Attempted Suicide		Completed Suicide	
	Unadjusted HR (95% CI)	**Adjusted HR (95% CI)** [a]	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)** [a]
Overall	2.09 (1.88-2.32)	2.14 (1.92-2.37)	1.76 (1.44-2,14)	1.85 (1.52-2.26)
Sex				
Men	1.97 (1.61-2.40)	2.01 (1.65-2.45)	1.64 (1.26-2.14)	1.73 (1.32-2.25)
Women	2.13 (1.89-2.41)	2.19 (1.94-2.48)	1.96 (1.46-2.64)	2.05 (1.52-2.75)
Year of entry				
68-80	2.06 (1.68-2.52)	2.18 (1.78-2.67)	2.06 (1.53-2.76)	2.14 (1.59-2.87)
81-90	2.53 (2.07-3.09)	2.58 (2.11-3.16)	1.92 (1.32-2.80)	1.96 (1.35-2.86)
91-00	2.03 (1.63-2.54)	2.02 (1.62-2.52)	0.99 (0.55-1.78)	0.99 (0.55-1.79)
01-12	1.85 (1.50-2.28)	1.86 (1.51-2.30)	1.98 (1.20-3.29)	1.98 (1.19-3.28)
Education				
Compulsory school or less	1.85 (1.53-2.24)	1.87 (1.55-2.25)	1.36 (0.96-1.92)	1.43 (1.01-2.03)
Upper secondary	2.40 (2.08-2.78)	2.45 (2.12-2.84)	2.00 (1.47-2.73)	2.08 (1.53-2.84)
Higher education	1.80 (1.38-2.34)	1.85 (1.42-2.41)	2.16 (1.34-3.49)	2.34 (1.45-3.78)
No educational data	2.14 (1.09-4.19)	2.18 (1.11-4.29)	2.03 (1.04-3.99)	2.12 (1.09-4.16)

[a]*Adjusted for sex, year of entry, education and region of residence at entry*

The results were similar in the sensitivity analysis in which subjects who attempted suicide before entry were not excluded from the analysis (data not shown). When stratified by duration after study entry, risk for attempted suicide was highest after >20 years among MS patients compared to the non-MS group, while risk for completed suicide was highest in the first five years. Despite some variation in risk of completed and attempted suicide in MS patients by disease duration, interaction testing did not identify statistically significant effect modification by duration (data not shown).

In a supplementary analysis, having >14 years of education (corresponding to the category of higher education) was associated with a lower risk for attempted suicide among both MS and non-MS groups compared to subjects with lower education. When the same analysis was performed for completed suicide, non-MS subjects with >14 years of education were shown to have a lower risk for completed suicide compared with subjects with lower education, while MS patients did not. In a sensitivity analysis was performed only on subjects entering the study after 1987, results were similar (data not shown).

4.4   STUDY IV

Subject characteristics are shown in **Table 5**. In general, the subjects were recently diagnosed with MS, without current active treatment, and had low EDSS and MADRS scores. Six subjects (13%) were diagnosed with MDD.

Table 5. Study IV. Cohort characteristics. Values are means with standard deviations if not otherwise stated.

Female (%)	n= 34 (66)
Age	35 (8)
Years since MS diagnosis	2.0 (3.1)
EDSS score	2.1 (1.1)
MADRS-S cognitive subscale score	4.4 (4.6)
Current major depression	n = 6
Current treatment for MS	n = 16
KIVS exposure to violence as child score	0.67 (0.94)
KIVS exposure to violence as adult score	0.72 (1.1)
IL-6 (pg/ml)	5.3 (9.7)
IL-8 (pg/ml)	45.0 (14.1)

EDSS = Expanded Disability Status Scale; MADRS-S = Montgomery-Asberg Depression Rating Scale, Self Report version; KIVS = Karolinska Interpersonal Violence Scale; IL = Interleukin

Median cytokine levels did not differ significantly between men and women or between depressed/non-depressed patients. Subjects with and without current treatment were also compared regarding cytokine levels and MADRS-S scores, without significant differences.

Correlations between cytokine levels and covariates are shown in **Table 6**. IL-6 correlated significantly with both total and cognitive MADRS-S scores, and with the KIVS score for exposure to violence as an adult. Levels of IL-8 did not show any significant correlations with other measurements.

Table 6. Study IV. Raw and adjusted correlation coefficients between cytokine levels and covariates, shown as Spearman's ρ with two-tailed p-values.

	IL-6				IL-8			
	Unadjusted	*p*	Adjusted*a*	*p*	Unadjusted	*p*	Adjusted*a*	*p*
Age	0.05	0.76	0.44	0.77	-0.12	0.42	-0.12	0.43
EDSS	0.13	0.38	0.14	0.37	0.09	0.56	0.11	0.47
MADRS-S cognitive	0.38	**0.011***	0.35	**0.017***	-0.15	0.32	- 0.14	0.37
MADRS-S total	0.41	**0.005***	0.41	**0.006***	-.091	0.55	-0.90	0.56
KIVS exposure to violence as a child	0.14	0.34	0.18	0.23	0.14	0.35	0.11	0.49
" as an adult	0.33	**0.025***	0.35	**0.010***	0.12	0.93	- 0.006	0.97

a adjusted for age and sex

*significant at *p*<0.05

EDSS = Expanded Disability Status Scale; MADRS-S = Montgomery-Asberg Depression Rating Scale, Self Report version; KIVS = Karolinska Interpersonal Violence Scale, exposure to violence; IL = Interleukin

Also, exposure to violence as an adult correlated significantly with MADRS-S cognitive score, and with MADRS-S total score when adjusted for sex and age. EDSS score correlated significantly with raw and unadjusted MADRS-S total score, and with the adjusted MADRS-S cognitive score.

Results from the multiple regressions are shown in **Tables 7a** and **7b**. In the analysis including MDD diagnosis, exposure to violence as an adult was significantly associated with IL-6 levels, while exposure to childhood violence and MDD diagnosis was not (MDD t=0.32, p=0.75). However, when MDD was replaced with MADRS-S cognitive score, exposure to adult violence only showed a trend towards significance (p=0.06). MADRS-S cognitive score was not significantly associated with IL-6 levels (t=1.47, p=0.15) in the analysis. The MADRS-S cognitive score did not have a significant mediating effect on the relation between KIVS scores and IL-6. Interaction variables were not significant in the models. In contrast, levels of IL-8 did not yield any significant associations in the regression analyses.

The sensitivity analyses where MADRS-S cognitive score were replaced with MADRS-S total score in the regressions yielded marginally different results and no changes in significance.

Table 7a. Study IV. Results from multiple regressions with a) IL-6 and b) IL-8 as dependent variables and exposure to violence as independent variable. Adjusted for major depression diagnosis (yes/no), KIVS scores, age, sex, and EDSS score.

	IL-6		IL-8	
	t	*p*	t	*p*
Exposure to violence as a child	1.30	0.20	0.26	0.80
" as an adult	2.43	**0.019**	-0.47	0.64

EDSS = Expanded Disability Status Scale; Self Report version; KIVS = Karolinska Interpersonal Violence Scale, exposure to violence; IL = Interleukin

Table 7b. Study IV. Results from multiple regressions with a) IL-6 and b) IL-8 as dependent variables and exposure to violence as independent variable. Adjusted for MADRS-S cognitive symptoms, KIVS scores, age, sex, and EDSS score.

	IL-6		IL-8	
	t	*p*	t	*p*
Exposure to violence as a child	1.06	0.30	0.61	0.55
" as an adult	1.88	0.060	0.13	0.90

EDSS = Expanded Disability Status Scale; MADRS-S = Montgomery-Asberg Depression Rating Scale, Self Report version; KIVS = Karolinska Interpersonal Violence Scale, exposure to violence; IL = Interleukin

5   DISCUSSION

5.1   METHODOLOGICAL CONSIDERATIONS

5.1.1   Register studies

Although the wealth of data available in Swedish national epidemiological and clinical registers brings many opportunities for research, there are also several considerations to be made. Observational studies, as opposed to experimental studies, can disclose statistically significant associations between the parameters studied but not causal relationships. Spurious associations may be made, regardless of the strength of the association. Thus, all results must be interpreted with caution. Furthermore, various types of bias may influence both the internal and external validity of the findings.

5.1.1.1   Selection bias

When the sampling of study subjects is influenced by an unknown factor associated with both the exposure and the outcome studied, selection bias has occurred. Studies I-III rely on the NPR, and study III also on the SMSreg, for the selection of MS patients. First, only specialized in- and out-patient care is recorded in the NPR and not care given in general practice/by family physicians. This means that there can be a bias towards patients with more severe MS in the study sample. Although it is assumed here that the absolute majority of MS patients in Sweden had at least one appointment with a neurologist during the years 2000-2005, patients with less disability may not seek care or only seek primary care.

In study III, patients were included from 1968 onwards. In earlier years coverage in the NPR was not complete and only in-patient care was recorded, and the latter brings further bias towards more severe disease. Furthermore, earlier versions of the ICD were used which are not always directly translatable to current versions. Also, the syndrome diagnosis of MS has evolved during the years[14] and earlier patients may have had a more obvious symptom presentation and severe disease in the lack of laboratory findings. Taking this into consideration, results from study III were also stratified by decade of diagnosis.

National coverage in the SMSreg is estimated at 80%, which means 20% of patients have not given consent or are not available for recruitment. Hypothetical reasons for this with potential bias could be not seeking specialized neurological care (i.e. less severe disease, or the opposite - palliative care), not being able to give informed consent (due to dementia or neuropsychiatric symptoms), or declining inclusion because of depression/fatigue.

Importantly, selection bias can also lead to surveillance bias, which means that observation for one condition increases the likelihood of detecting another, which has great implications when studying comorbidity. Comparisons between risks for psychiatric diagnoses in study I, for example, are most likely biased by this, and by lack of primary care data.

Finally, another form of selection bias may be differences in "loss to follow-up" in cohort studies, meaning for example that a different proportion of MS patients than comparison subjects may have died or moved abroad in study III, or that MS patients with psychiatric comorbidity may have died in a greater proportion in the survival analysis in study I.

5.1.1.2 Misclassification bias

Misclassification bias is a type of information bias, i.e. that a measurement error introduces bias. If this error is systematic across the studied groups, the studied effect becomes smaller. If not, bias is introduced. The most likely source of misclassification bias in studies I-III are the ICD diagnoses. Regarding MS diagnosis, the accuracy in the SMSreg is high[239], while the NPR generally has an acceptable degree of diagnostic accuracy[252] although MS has not been examined specifically. Regarding the psychiatric diagnoses, very few have been validated in the NPR, with varying but mostly acceptable results[253-255]. Notably, depressive disorders and anxiety diagnoses have not been validated. Also, self-harm with non-suicidal intent can also be misclassified as a suicide attempt[256], and this classification has not been validated in the NPR either. Deaths with undetermined intent were not included in order to increase validity in study III.

A known MS diagnosis could also lead to less reporting of psychiatric diagnosis (i.e. the physician sees depression as a phenomenon of the MS disease and does not record a separate diagnosis, or does not bother to register secondary diagnoses at all). Psychiatric diagnoses among MS patients are probably underreported in this study, which is supported by the observation that the corresponding figures for pharmacological treatment in study I are generally higher.

For validation of public health records psychiatric diagnoses among MS patients, a combination of diagnostic data and pharmacological prescriptions has been used in some studies to increase validity[257]. This approach was not used in study I, where instead diagnoses and pharmacological data were analyzed separately.

Also, education level was used as a covariate in studies I-III, with up to 5% of subjects with missing data. These subjects may, for example, have immigrated to Sweden. A small percentage of subjects with missing baseline data were excluded in study I, which could have introduced a selection bias as being born outside of Sweden was somewhat less common among MS patients.

5.1.1.3 Confounding and mediation

A confounder is a factor associated with both the exposure and the outcome in a relationship, while a mediator lies on the causal pathway between exposure and outcome. In order to prevent confounding, a number of sociodemographic covariates were adjusted for in the analyses I-III, and closely matched controls were used as comparison cohort in studies II and III.

The most important mediator of interest regarding most of the outcomes studied in studies I-III is probably physical disability status, which we did not have information on – although, as repeatedly stated in the Introduction section of this thesis, the association between disability and psychiatric comorbidity in MS is still not wholly clear. Additionally, this data would have been of limited use in the comparisons with non-MS subjects used in these studies, as they by definition could not be assessed with MS-specific disability measures (most commonly the EDSS).

5.1.1.4 Validity of the chosen outcomes

In study I, being granted DP was chosen as a measure of impact of disability. Although, as discussed in the Introduction, being outside the labor market is often associated with physical disability, it is by no means directly translatable, and should not be interpreted as such. Also, no clinical studies on the specific characteristics of MS patients who are granted DP exist. In study II, only subjects with full-time DP were selected for comparison. As being granted DP is often a gradual process in Sweden, with patients going from sickness absence to partial to fulltime DP, this might have diluted the value of this patient selection variable.

In studies I and II prescriptions of pharmacological data are used as a proxy for psychiatric morbidity. An advantage of this measure is that misclassification issues related to registered diagnoses discussed above do not arise; however, the studied drugs may be used for several disorders (e.g. SSRIs for both anxiety and depression) and may also be used for other purposes than psychiatric symptoms/disorders. SSRIs are also used to treat pathological laughing and crying in MS patients[133], something that affects only a minority of patients with advanced disease. Benzodiazepines are also a last line choice for treating spasticity[258], a symptom which could reduce work capacity in MS patients.

We compared the ratio of patients being prescribed psychiatric drugs as a binary measure instead of using the continual measure of, for example, Defined Daily Dosages (DDDs). In regard to the size of the study sample, this leaves the analysis less sensitive to outliers (i.e., large consumers of benzodiazepines and sleeping agents). It could also be argued that a dichotomous category of presence/absence of prescribed psychiatric drugs has a different and perhaps more accurate construct validity in measuring psychiatric morbidity on a population basis than measuring DDDs, as even singular prescriptions signify an intent to treat psychiatric morbidity. MS patients are quite sensitive to side effects from psychiatric medication which could lead to a higher number of interrupted treatments.

5.1.1.5 Statistical conclusion validity

A type II error means not detecting an association in a test although it is present, and the concept is closely connected to that of statistical power. As they are based on registers with approximately nationwide coverage, studies I-III are well powered statistically which is necessary for detection of rare outcomes. Even so, some of the outcomes measured in study I (such as personality disorder diagnoses among MS patients not on DP) were only detected in a small number of patients, which means CI are wide and that the conclusions that can be

drawn from these observations are limited. In study II, OR were wide and overlapping between the different study groups; however, the trends were fairly clear. Suicide is, thankfully, a relatively rare outcome among both MS patients and the general population, but this also means that the stratification of data in study III brings lower statistical power.

A type I error means detecting a statistically significant association which is not there, and this is closely related to the level of alpha chosen for the test - typically 0.05, which roughly translates to a 5% risk of finding a false association. Repeated measurements, and an increasing number of covariates tested, increase the risk for a type I error, and in study I this was adjusted for with a Bonferroni-Holm correction of the alpha value.

5.1.1.6 *External validity*

These studies have the strength of being based on national, high quality registers with in most cases very high completeness. However, as these studies are based solely on data from Sweden, the generalizability to other populations could be questioned. Genetic and geographical differences are known among MS patients worldwide. Treatment regimes and health care systems vary between countries. Especially psychiatric diagnostic traditions and prescriptions patterns show wide differences internationally (see for example [196, 259]). As national health policies change, data may also not be valid over time.

Sweden has a well-developed health insurance system, which may not be readily comparable to many other countries. The cross-section design in study II may have been sensitive to yearly trends in being granted DP, which could be influenced by contemporary agendas in national politics. On the other hand, the method has the advantage of not being sensitive to trends in pharmacological prescriptions.

5.1.2 Clinical study

5.1.2.1 *Selection and misclassification bias*

The subjects in this study were selected according to several criteria and do not represent a natural sample of MS patients. MS diagnosis and disability score was clinically verified. Several measures of depression were applied in order to limit the risk for misclassification and subjectivity in the diagnosis. There is always a risk for recall bias regarding historical data, as for exposure to violence in this study, and there is the risk that, for example, current depression influences this recall bias.

As described in the introduction, CSF detection and levels of cytokines vary widely between studies, and the accuracy and reliability of sampling within or between MS subjects is little studied. We cannot say how large the sampling error is in this study, or if it is influenced by e.g. cytokine levels, and thereby introducing bias. The sampling in this study was not standardized regarding e.g. food intake or time of day, which increases the uncertainty.

5.1.2.2 Confounding and mediation

The analysis in this study was adjusted for age, sex, and disability status, which could be significant confounders. Depressive symptoms were investigated as a mediator in this study but not found statistically significant; however, this could be a type II error.

5.1.2.3 Validity of chosen exposures and outcomes

IL-6 and IL-8 were chosen as immune markers due a combination of properties: well established roles in the innate immune response, a repeatedly proven association with psychiatric symptomology (especially IL-6) including suicidality and exposure to adversity, and a decent detectability in previous studies on MS patients.

In this study we chose several measures of depression, of which the semi-structured, clinician-rated interview is considered the gold standard. The MADRS-S is also a well-established measure of self-rated depression with the advantage that it closely follows the DSM criteria for MDD. To avoid collinearity we primarily analyzed only cognitive self-rated symptoms of MDD which also pointed out some differences in the results compared to when all symptoms were included.

Exposure to violence is a type of adversity which has not been investigated previously in MS patients. We do not know if or how exposure to interpersonal violence, especially of the low-grade type most common in this study, differs from other kinds of stress regarding the association with depression and IL-6.

5.1.2.4 Statistical conclusion validity

This study was probably underpowered regarding performing a logistic regression analysis with all covariates included. An option would be to perform a backwards regression, which would exclude non-significant variables such as age and sex, thus increasing significance. This could, however, decrease the validity of the analysis. The number of patients with MDD diagnosis in the sample was unexpectedly low considering previous research. However, the association between IL-6, depressive symptoms and especially exposure to violence in adult life was rather clear throughout the study.

5.1.2.5 External validity

This study was performed on a highly selected sample of MS patients, with low levels of self-rated depression and MDD diagnoses, short disease duration, and low disability scores. Although this is a well-characterized sample, and the newly diagnosed group of MS patients is clinically relevant to study, we cannot determine the generalizability of the results regarding MS patients as a whole. The findings regarding IL-6 are, however, supported by the existing literature on non-MS patients.

5.2   IMPLICATIONS OF RESULTS

5.2.1   An elevated risk for psychiatric diagnoses and medications

To our knowledge, this is the first comprehensive mapping of all types of psychiatric diagnoses and drug classes in MS patients. Depressive disorder was, as expected, the most common psychiatric diagnosis among both MS patients and non-MS individuals of working age. The 4.4% of MS patients who had been diagnosed with depression during the five years studied is a rather low proportion compared most studies[25], but as discussed in section 5.1.1.1, diagnoses from primary care are not included in this study. Furthermore, most previous estimates of prevalence of psychiatric diagnoses are based on survey or clinical studies, which seem to lead to higher estimates. The exclusion of patients over 65 years of age is another possible contributing factor. The risk for bipolar disorder was nearly doubled in MS patients compared to non-MS individuals, but the prevalence of 0.5% was lower than in other studies[127, 260]. The risk for obtaining a psychotic disorder diagnosis was not statistically significant in MS patients with a 0.8% prevalence, in line with the only previous register study on this topic [22].

In study I, 35% of all MS patients were prescribed a psychiatric medication during the six months observed, which was a high number compared to non-MS individuals. The most common drug class in the study, SSRIs, was prescribed to 17% of MS patients which suggests a high prevalence of depressive disorder and anxiety disorders. Of note is that depression has been suggested to be generally underdiagnosed and undertreated in MS patients[261, 262], which indicates that the prescription rates would perhaps be even higher if MS patients were to receive adequate antidepressant treatment. The tripled risk for benzodiazepine prescriptions seen here should be considered problematic, since there is a well-known risk for unwanted side effects and dependence, and this drug class not being recommended at all in modern clinical guidelines for anxiety disorders[263].

Together, these results suggest that analysis of drug prescription data can be used as a proxy for psychiatric comorbidity by itself or in combination with diagnostic data, and that an elevated risk for almost all kinds of psychiatric comorbidity among MS patients is apparent.

5.2.2   Psychiatric comorbidities increase the risk for disability pension

In the survival analysis of study I, psychiatric diagnoses and medications were generally associated with a substantially higher HR for DP among MS patients. Depressive disorders were the diagnoses associated with the highest absolute number of patients being granted DP, further supporting the notion of the detrimental consequences of this comorbidity. It is, however, not possible to establish whether this is due to a causative effect of depression, or if the elevated rate of depressive diagnoses is due to a psychosocial reaction to an increased general disability which in itself eventually leads to DP. Considering the high costs for the

individual and for society that is associated with being granted DP, this should be considered a priority in future research.

Although few in absolute numbers, personality disorders were the diagnoses with the highest HR for DP, which could be mediated by coping difficulties often present in personality disorders[264], but also by the fact that cognitive impairment is overrepresented in this group[129] among MS patients. The diagnosis group of organic and developmental disorders, which includes neuropsychiatric conditions considered to be secondary to an organic disease, also increased the HR for DP substantially. This group is heterogeneous and could for example reflect the disabling effects of conditions associated with latter stages of MS mentioned in section 1.2.6.

Among the medications, antipsychotics were associated with the highest HR for DP, reflecting the serious nature of the conditions often treated with this class of drugs, namely bipolar disease and psychotic disorders. Additionally, the side effect profile of these medications, including various anticholinergic effects and extrapyramidal symptoms, could be especially unwanted in MS patients, and a causal contributing effect cannot be ruled out. This should also be considered regarding the elevated risk for MS patients treated with benzodiazepines.

These results expand the existing knowledge on the synergistic effect of MS and psychiatric comorbidity on risk for DP, and suggest future research directions targeting depression, anxiety, and personality disorders to decrease individual and societal costs of DP.

5.2.3   Disability pension and association with prescriptions of psychiatric drugs

Study II shows that there are differences in the risk for being prescribed psychiatric drugs between MS patients and controls in the years before and after being granted DP. The fact that MS patients had higher rates of SSRIs after DP compared to controls, and that the rates of benzodiazepines increased after DP in MS patients, could be interpreted as DP not having an alleviating effect on the mental health burden in MS patients. It could also be that DP in itself adds to psychiatric morbidity in MS patients. Since clinical disability data was not available for this study, we cannot say whether progression of disability is reflected in the results, leading to increased prescriptions of psychotropic drugs.

Being granted DP does not seem to have a beneficial effect on MS patients' mental health in this study. A non-significant decrease in risk for both SSRIs and sleeping agents was seen among those on DP since 1-2 years, but not among those on DP since 3-6 years, which could stand for a brief relief of psychiatric burden after DP which is not lasting. Conversely, the non-MS controls on DP had lower risks for SSRIs compared to those not yet on DP, with the risk actually decreasing the more years they had been on DP. Considering that a third of the non-MS controls had mental DP diagnoses, the fact that MS patients still had a comparatively higher relative risk for being prescribed SSRIs after DP is noteworthy.

The majority of non-MS controls in this study had mental or musculoskeletal DP diagnoses, of which the most common (depression, musculoskeletal pain) usually do not have a progressive course. Most MS patients will sooner or later enter a progressive phase of the disease which could perhaps explain the differences in SSRI and benzodiazepine prescription after DP seen here compared to non-MS DP controls. However, patients with progressive stages of MS have not been shown to have higher rates of depression than patients with RRMS; there are even some contrary results. There is the possibility that DP itself contributes to the psychiatric burden in MS.

Taken together, these results show that the risk for being prescribed drugs for depression and anxiety do not decrease among MS patients after DP, and also that this relationship differs when compared to non-MS controls. The perceived role of DP as a relief for MS patients warrants further consideration.

5.2.4   An elevated risk for attempted and completed suicide

Study III replicates previous research findings regarding the elevated suicide risk among MS patients in the largest cohort to date. Furthermore, an elevated risk for attempted suicide is demonstrated. This study also showed that the inverse association between higher education and completed suicide, as seen in the comparison cohort, was not present in MS patients. This risk difference could be due to chance, as the absolute number of suicides among MS patients with >14 years of education was low (n=14), but could also suggest that consideration should be taken in monitoring suicide risk among MS patients with higher educational attainment, as they could be clinically perceived as low-risk patients.

The elevated risk for attempted and complete suicide was constant regardless of decade of study entry, except for completed suicide in the 1990s. Considering the advancement of MS treatments during the last decades, this is somewhat unexpected. The risk for completed suicide was highest among newly diagnosed MS patients, and the risk for attempted suicide highest after >20 years of disease. This suggests that attention to signs of depression and/or suicidality is even more warranted in these groups.

As the elevated risk for suicidality in MS patients should now be considered well established, future research should focus on exploring possible mediating factors such as clinical course, pharmacological treatment and response, psychiatric and somatic comorbidity, and socio-economic characteristics.

5.2.5   Association between IL-6, depression and exposure to adult violence

The main finding of study IV is that depression and exposure to adulthood violence is associated with CSF expression of IL-6 in MS patients. Although levels of exposure to violence was low in this study, and comparisons to non-MS patients should be made with caution, this is theoretically supported by the existing literature on stressful events and changes in IL-6 regulation in non-MS subjects in both blood and CSF. There is also a possible connection with the established association between stressful life events and MS

exacerbations. The molecular basis, however, remains to be determined, but may include effects mediated by adaptive, innate and glucocorticoid responses[265].
Importantly, IL-6 levels have been suggested to also increase sensitivity to stress, which theoretically could imply a central role in both activation and maintenance of a stress cycle. We do not know if or how exposure to interpersonal violence, especially of the low-grade type most common in this study, differs from other kinds of stress regarding these mechanisms.

This is, to our knowledge, the first demonstration of an association between external adverse events and an immune marker in MS patients. This has previously been reported in psychiatric populations, such as patients with MDD[266], and in patients with somatic disorders such as rheumatoid arthritis[194] and migraine [267]. For MS patients, this could have potential implications. For example, informative biomarkers are warranted for diagnostic, prognostic or therapeutic purposes[268], and could also be used for treatment decisions[269]. If there is an association between external stressful events and immune system regulatory mechanisms as demonstrated in this study, it suggests that potential immune system biomarkers must be evaluated only when known interactions between psychiatric symptoms and stressful events are carefully considered in order not to bias their interpretation.

The findings in this study suggest that areas of future research should include the relation between stressful events, inflammatory response, MS incidence and long term MS prognosis.

5.3 ETHICAL CONSIDERATIONS

The studies included in this thesis were all approved by the Regional Ethics Committee at Karolinska Institutet, approval no. 2007/1762-31, 2009/1917-32, 2010/466-32 (studies I and II), 2013/1156-31/5, 2013/1973-32 (study III) and 2012/352-31/4 (study IV).

Studies based on administrative registers do not entail any individual effort from the subjects studied, but there are ethical issues considering the integrity of individual data, the conclusions that can be drawn from register data, and security and cost issues of data management (see Ludvigsson et al[270] for an extended discussion). Clinical registers such as the SMSreg, however, do require an informed consent for participation, and also warrants extra data collection registration for the purpose of health care quality control and/or research. The possible benefits of this should be weighed against the administrative cost and the individual efforts from the participating patients.

In clinical studies, the cost-benefit ratio for the participating subjects must be considered carefully. In study IV in this thesis, MS patients gave informed consent to participate in a special appointment for a clinical interview and to complete a self-rating scale. Answering questions regarding past adverse events and psychiatric symptoms may in some cases elicit feelings of discomfort and psychological distress. All patients who were considered in need

of psychiatric follow-up, and consented to it, were referred to appropriate care. All patients were informed of the possibility of a follow-up telephone contact with the interviewing psychiatrist. The study was designed so that no extra lab tests or examinations were needed outside of ordinary clinical practice. A possible benefit for the participating patients was the identification and treatment initiation of psychiatric symptoms.

5.4   GENERAL DISCUSSION AND FUTURE DIRECTIONS

The studies in this thesis look at psychiatric comorbidity in MS patients from methodologically different angles; as an exposure, with DP or immunomarkers in CSF as outcomes, or as outcome compared to non-MS patients, or in relation to DP. The question of MS and psychiatric comorbidity is complex, and this thesis has probably not helped simplifying the matter – with the possible exception that we may with even greater certainty state that *psychiatric comorbidity is overrepresented among MS patients, and worsens the outcome for the patients in several pivotal ways.*

This thesis starts with an attempt to review the current literature on psychiatric comorbidity in MS, and it soon becomes utterly clear that important pieces of the puzzle are missing. A major problem is that both MS and psychiatric disorders are syndromes with a great heterogeneity in their clinical presentation, and not etiological diagnoses. When studying these conditions, we are not sure that any two patients share the same underlying pathology, only that their presenting symptoms are (somewhat) similar. Furthermore, we are not helped by the fact that some of the most common and important symptoms in MS patients that mediate psychological distress, such as fatigue, pain, and sleeping problems, lack operational criteria.

In the last few years, a number of interesting studies based on Scandinavian registers have looked retrospectively at MS patients in the years before diagnosis. Looking at Norwegian conscription data, men who would later develop RRMS or PPMS scored significantly lower on IQ tests than comparators – and for PPMS patients, differences were significant up to 20 years before first diagnosis[80]. In a Swedish conscription cohort, men with MS had lower physical working capacity in adolescence - but this study did not show significant differences in cognitive function and stress resilience scores between cases and controls[271]. Moreover, patients in the SMSreg had significantly higher rates of both sickness absence and DP up to 15 years before MS diagnosis compared to matched controls[272].

These results highlight the question if there is a psychiatric phenotype among MS patients before diagnosis, with or without presence of other symptoms. Johansson et al[53] demonstrated that genetic liability could not explain the strong positive association between MS on one hand, and MDD and type I bipolar disorder on the other. However, the underlying factors for psychiatric disorders may be more complex than observation of distinct categorical entities may reveal. Given the high rates of comorbidity observed in psychiatric patients, and growing evidence that current psychiatric nosology may not adequately explain

occurrence and co-occurrence of psychiatric morbidity, Caspi et al[273] examined the notion of a "p factor", i.e. an underlying dimension to the risk of developing all forms of common psychopathology, in a well-characterized longitudinal cohort. Higher scores on this dimension were associated with greater life impairment, worse developmental histories, and more compromised brain function in early life. It would be very interesting to see whether such a model would be applicable also to MS patients regarding occurrence of psychiatric symptoms, but also whether such an underlying factor would somehow be related to the occurrence and outcomes of MS in itself.

The importance of functional coping styles has been well established in later years of MS research, and would be interesting to explore as a mediator for all outcomes in this thesis, diverse as they may be. Coping mechanisms in MS patients have been linked to such varied outcomes as depression[274], fatigue[275], unemployment[276] and suicidal ideation[75]. Identifying MS patients with non-functional coping styles seems to be a priority. However, taking into account the results from study IV in this thesis, and in line with the reasoning above, coping style as a personality trait should perhaps also be explored as risk factor for developing/worsening MS.

The role of stress as a risk factor for MS has been explored historically as described in section 1.2.7. What if persons who react non-functionally to adverse events pre-MS diagnosis are at greater risk for developing changes in the immune response after such events, and this could be a contributing factor to development of MS? And could an innate predisposition for non-functional coping also mediate the high prevalence of some types of psychiatric comorbidity in MS, and hence work as a confounder? The only way to thoroughly answer this research question would be through case-control studies using cohorts where coping styles have been examined in a large number of subjects, preferably before the typical age of MS onset. If MS patients have different coping styles than other persons with disability or chronic diseases, this might also explain the lack of beneficial effect of DP on psychiatric morbidity seen in study II. This reasoning is summarized in **Figure 5**.

In summary, future research on risk factors for, and consequences of, psychiatric comorbidity in MS faces several challenges. Current nosological psychiatric classification may not be adequate for describing the psychiatric symptoms in MS, which poses a real problem since register based research often depend on diagnoses. Clinical registers such as the SMSreg and its equivalents from other countries may insure the collection of clinical parameters such as disability data, rating scales and cognitive screening tests. Functional outcomes of value both for the patient and for society must be identified and evaluated further, and sickness absence and DP data could be considered strong candidates. Also, risk factor identification for MS, including possible connections to premorbid personality or functioning, depend on case-control studies, where large population scale studies and register research could prove to be of further use. It is not enough to state a high risk for detrimental outcomes such as DP or suicide among MS patients; further identification of risk factors is warranted with the purpose

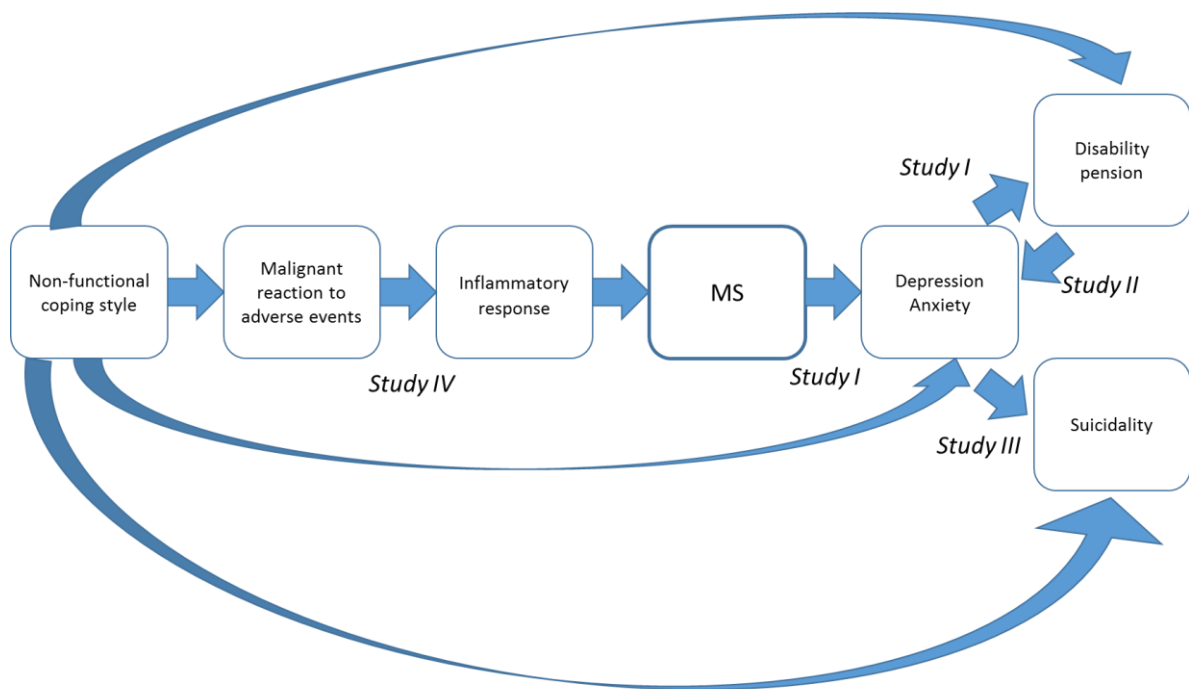of constructing adequate clinical screening tools and, ultimately, clinical measures, to prevent them.

Figure 5. A conceptional model of findings in this thesis, with the proposed addition of non-functional coping as a mediating factor.

6 CONCLUSIONS

We conclude that there is an elevated risk among MS patients for psychiatric comorbidity including attempted and completed suicide, that the presence of psychiatric comorbidity increases the risk for disability pension, that disability pension may not be associated with a relief of psychiatric burden as in non-MS patients, and that exposure to violence in adult life and depression is associated with changes in the immune system among MS patients. Proposed targets for future research include early detection and treatment of various kinds of psychiatric comorbidity as well as identification of risk factors, as well as measures for staying in the labor market. The association between life adversity and neuroinflammation should be further explored.

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