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Risk factors for infections in people with multiple sclerosis

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Zusammenfassung

Multiple Sklerose (MS) ist eine entzündlich-demyelinisierende Erkrankung des zentralen Nervensystems, die aufgrund ihres Beginns im jungen Erwachsenenalter und der möglichen Funktionseinschränkungen im Krankheitsverlauf eine hohe Belastung darstellt. Das Risiko für Infektionen ist bei MS im Krankheitsverlauf erhöht, was nicht nur zu einer weiter verminderten Lebensqualität, sondern möglicherweise auch zu einer erhöhten Krankheitsmorbidität führt. Daher ist die frühzeitige Erkennung von Personen mit hohem Infektionsrisiko von besonderer Bedeutung. In dieser Studie wurden 19 Kovariaten auf ihren Zusammenhang mit der Häufigkeit von Infektionen untersucht. 389 Patienten mit MS oder klinisch isoliertem Syndrom aus Innsbruck und Helsinki wurden retrospektiv mit einem Fragebogen über die Häufigkeit von Infektionen der oberen Atemwege und der Harnwege in den letzten zwei Jahren befragt. Für die Variablenauswahl wurde ein schrittweises Regressionsmodell an 203 Patienten aus Innsbruck trainiert und an 87 aus Innsbruck und 76 aus Helsinki getestet. Die wichtigsten Variablen zur Vorhersage der Infektionshäufigkeit waren weibliches Geschlecht (IRR = 2,51), progressiver Krankheitsverlauf (IRR = 1,50), chronische Lungenerkrankung (IRR = 1,86), hohe Leukozytenzahl (IRR = 1,31) und Blasendysfunktion (IRR = 1,58). Die Vorhersagegenauigkeit ist bei beiden Stichproben ähnlich. Die wichtigsten Limitationen dieser Studie sind das retrospektive Design, sowie der Zeitrahmen während der SARS-CoV-2-Pandemie, in der man Abstand halten und Schutzmasken tragen musste. Folgende Studien mit größerer Stichprobe sollten sich auf die verschiedenen zur Behandlung verwendeten Substanzen sowie auf protektive Faktoren konzentrieren. Insgesamt ermöglicht diese Studie eine vorläufige Risikoeinschätzung für die individuelle Infektionsanfälligkeit, welche zukünftig einen wertvollen Beitrag zur klinischen Entscheidungsfindung beitragen kann.

Schlüsselwörter: Multiple Sklerose; Risikoscore; Obere Atemwegsinfektionen; Harnwegsinfektionen; Vorhersagemodell

Abstract

Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system with a high burden of disease due to its onset in young adulthood and possible functional impairment in the course of the disease. The risk for infections is increased with MS resulting not only in a decreased quality of life, but also potentially in an increased disease morbidity. Thus, early identification of high risk individuals for infection is particularly important. This study investigated 19 covariates regarding their association with the frequency of infection. 389 patients with MS or clinically isolated syndrome from Innsbruck and Helsinki were surveyed retrospectively with a questionnaire about their amount of upper respiratory tract and urinary tract infections within the past two years. For variable selection, a stepwise negative binomial regression model was trained on 203 patients from Innsbruck and tested on 87 from Innsbruck and 76 from Helsinki. The most important variables to predict the frequency of infection were female sex (IRR = 2.51), progressive disease course (IRR = 1.50), chronic lung disease (IRR = 1.86), high leukocytes (IRR = 1.31), and bladder disturbance (IRR = 1.58). Predictive accuracy is similar in both test samples. The main limitations are the retrospective design and the time frame during the SARS-CoV-2 pandemic in which people were obligated to social distancing and to use face covering masks. A future study on a larger sample should focus on the different substances used for treatment as well as protective factors. Overall this study paved the way for a preliminary risk score to assess any patient's individual infection risk, providing valuable insights for clinical decision making.

Keywords: multiple sclerosis; risk score; upper respiratory tract infections; urinary tract infections; prediction model

Eigenleistung

Für die Erhebung an der Univ.-Klinik für Neurologie der Medizinischen Universität Innsbruck wurden etwa 150 PatientInnen von mir in der Ambulanz eingeschlossen. Die andere Hälfte wurde von Sonja Maierbrugger akquiriert. Der zur Erhebung verwendete Fragebogen sowie der Ethikantrag wurden von Harald Hegen und Franzsika Di Pauli erstellt. Bei der Erhebung an der neurologischen Ambulanz der Universitätsklinik Helsinki wurden die Fragebögen von mir verpackt und verschickt. Die demographischen Informationen und Laborwerte wurden durch mich aus dem nationalen Register extrahiert. Die spätere Dateneintragung der Fragebögen erfolgte ebenfalls durch mich. In Helsinki wurden etwa 30 PatientInnen direkt durch Telefonate von Ella Finne erhoben, die außerdem für die Übersetzung des Fragebogens in Finnisch und Swedisch verantwortlich war. Die notwendige Infrastrukturen und Materialien sowie die Erlaubnis der Klinik in Helsinki wurden von Sari Atula und Sini Laakso organisiert. Sämtliche statistischen Auswertungen wurden selbstständig ausgewählt und durchgeführt. Auch die in dieser Arbeit erstellten Texte wurden eigenständig verfasst.

1 Background

1.1 Multiple sclerosis

Multiple sclerosis (MS) is a currently incurable inflammatory, demyelinating disease of the central nervous system (CNS). It is the most frequent cause for (non-traumatic) neurological disability in young adults [1, 2]. In most patients, the symptoms develop between 20 and 40 years [2]. The autoimmune reaction leads to an inflammation of the CNS, resulting in white-matter demyelination as well as small lesions in grey matter cortices [1, 2]. While these lesions are often completely reversible in the beginning of the disease, they can result in meaningful physical and cognitive disability in the later course. Clinical presentation of MS is heterogeneous depending on the location of the lesions, but typical symptoms include mobility problems, chronic pain, spasticity, fatigue, bladder and bowel dysfunction, sexual dysfunction, numbness and tingling in the extremities, tremor, loss of strength and coordination, visual impairments, and hypersensitivity to heat [3, 4]. While the cause of MS is still unknown, the current hypothesis assumes environmental risk factors in genetic predisposed individuals [1, 5].

In most cases, multiple sclerosis starts with a relapsing course. Usual symptoms include isolated sensory deficits, cerebellar dysfunction or an opticus neuritis. A relapse is characterized by symptoms that last at least 24 hours, after a minimum of 30 days since the last relapse [6]. 10 to 20 years after symptom onset, 75 % patients with an initial relapsing-remitting disease course develop a secondary progressive form, where diffuse inflammations lead to a continuous loss of function [6]. In 10-15 % of people with multiple sclerosis (PwMS) the disease course is progressive at onset [1]. For progressive courses, spinal symptoms such as gait ataxia, paresis, and spasticity are most common [6]. Various disease modifying treatments (DMTs) exist to modify the disease course. This mainly applies to relapsing-remitting multiple sclerosis (RRMS), whereas efficient treatment options for progressive forms are still limited [7, 8]. Despite progresses in pharmacological treatment, disease-adjusted life years (DALYs) decreased only slightly from 1990 to 2016 with a total of 1,151,478 in 2016 [3].

In addition to the symptoms caused by the inflammation of the CNS, there are several typical comorbidities in PwMS. The most common are depression, anxiety, cerebro- and cardiovascular diseases, diabetes, thyroid diseases as well as inflammatory bowel diseases [9, 10]. An increased risk of cancer, which has been discussed in the past, is considered unlikely in current research [9, 11]. Especially diabetes, hypertension, and chronic obstructive pulmonary disease (COPD) might lead to an accelerated disability progression [9]. Living with a comorbidity in addition to the symptoms of MS influences the burden of disease and quality of life negatively [9].

In general, the burden of disease is high in PwMS, due to the early onset and incisive functional impairment in the course of the disease [12]. There are many factors decreasing the quality of life, but fatigue, cognitive impairment, and pain are consistent across many studies [12]. There is also a gap in employment between PwMS and the general population, although on average it has been decreased in the last decade [13]. The problem remains that after 10 years only less then 20 % of PwMS still work [4].

Besides self-reparation within the nervous system, diverse rehabilitation strategies have been proposed. These strategies still lack strong evidence for their supportive effect, as a recent Cochrane review exemplified [14]. A multidisciplinary approach (with physiotherapists, occupational and speech therapists, neuropsychologists, and social workers) showed moderate evidence to reduce disability and improve continence-related quality of life [14]. The extent to which this is more efficient than physiotherapy alone is unclear [14]. Another rehabilitation strategy with moderate evidence were information provision interventions, which served to promote informed choices [14]. The high prevalence of MS also brings a significant socioeconomic burden. In the United States alone MS costs more than 10 billion dollars per year [1]. This is not only a result of costly treatment options and years of sick leaves with rehabilitation, but also early pension caused by functional disability. As a result of the combination of the symptoms, comorbidity, and often either immunosuppressive or immunomodulatory treatments, the risk of infections is increased in PwMS [15]. This is not only relevant because it further alters the quality of life, but because infections can worsen relapses or lead to exacerbation [16]. Hence, it is of central interest to identify patients with a high risk for infections to not only increase the quality of life, but also to support existing treatments in disease modification. This study investigated potential risk factors to detect PwMS and PwCIS with a high risk of infections. The results can be used as a preliminary risk assessment to make more informed decisions about infection risks in clinical practice.

1.1.1 Epidemiology

Worldwide there are more than 2.2 million people diagnosed with MS [3]. 85 % of diagnoses start with a relapsing-remitting disease course, which often turns into secondary progressive form, while around 15 % have a progressive course from onset [1, 17, 18]. The mean age of diagnoses is 30 years, while the mean age of all patients is about 50 years [19]. Around 70 % of all patients are female [e.g., 18–21].

Prevalence. The median of the global prevalence slightly increased from 9.1 to 11.8 per

100,000 by 10.4 % from 1990 to 2016 [3]. There are large differences in prevalence geographically with the highest in high-income countries with temperate climate, where Caucasian people of Nordic origin live [19]. While the prevalence is 127 and 165 per 100,000 in Europe and North America respectively, only 2 to 3 persons per 100,000 are diagnosed with MS in sub-Saharan Africa and Oceania [3]. The prevalence for Australasia is around 91 per 100,000 [3]. The estimated prevalence rates within the continents and countries are heterogeneous [17]. For example in North America, in Lubbock (United States of America) the estimated prevalence is 39.9 per 100,000 until 2007, whereas the highest was found in Saskatchewan (Canada) with 313.6 per 100,000 in 2013 [17, 22]. Although this latitudinal gradient was smaller after standardization [19].

For this study, the prevalence in Austria and Finland are most important. In Austria, there are more than 13,000 PwMS and PwCIS, from which around 1,500 patients are treated at the MS clinic of the Department of Neurology of the Medical University of Innsbruck [23]. This results in a prevalence ratio of 159 per 100,000 in Austria [23]. In Finland, the nationwide prevalence is estimated to be 180 to 200 per 100,000 in 2018 counting more than 10,000 patients [18]. There are large regional differences with the highest prevalence in Southwest Finland of around 280 per 100,000 in 2018 and 168 per 100,000 in North Karelia [18, 21]. More than 2,400 of the Finnish patients are treated in the Helsinki and Uusimaa district [18]. The increase in prevalence is considered to be caused largely by more accurate and earlier diagnostics, better treatment options, and longer survival times, which result in an older age of the patients [19, 24]. The life expectancy is reduced by 6 to 10 years for PwMS compared to the healthy population [24]. The dependence on health care and availabilities of registers in the countries make prevalence a biased estimate. However, the incidence is not constrained by those biases [19].

Incidence. The global incidence of MS is 2.1 per 100,000 PY [25]. The incidence has been relatively stable with a few exceptions. For example, Koch-Henriksen et al. found an increase from 5.91 in 1950 to 12.33 in 2009 in Danish women [26]. This hints at environmental risk factors due to lifestyle changes in the past decades [19]. In Finland the only meaningful change in incidence was in 1990, which can mostly be explained by an increased usage of MRI for diagnosis [21, 27]. This relatively stable incidence rate means that the higher prevalence over time is largely caused by a higher female-to-male ratio with longer life expectancies in females [3, 18]. In Austria the incidence rate was 19.5 per 100,000 PY in 2017 and in Southwest Finland at 12.1 per 100,000 PY in 2016 [28]. Note that the observed numbers are usually smaller

compared to prevalence studies, which might lead a to larger uncertainty of the incidence estimates [19].

1.1.2 Pathogenesis and etiology

The cause for multiple sclerosis is still largely unknown, but the understanding of the pathogenesis has been improved significantly in the past decades. MS is caused by autoimmune responses from the innate and adaptive immune system, leading to white-matter demyelination and lesions within grey matter cortices [1]. Furthermore, axonal and neuronal damage are caused, inter alia, by oxidative stress and mitochondria defects [1, 5]. Oligodendrocytes produce limited remyelination, while the reactive proliferation of astrocytes leads to plaques [1, 5]. These plaques describe scars in the glia cells, which are small in the beginning, but merge over the course of the disease [5]. The adaptive immune system has been identified as particularly important in the pathogenesis [29, 30]. In the lesions, CD4+ helper as well as CD8+ cytotoxic T cells were found [1, 5]. It is hypothesized that defective regulatory T cells are causing the accumulation of effector T cells in the central nervous system [30].

B cells also play a critical role in the pathogenesis [29]. These B cells stimulate inflammation and thus produce oligoclonal bands, which have been successfully used for diagnostic purposes in MS [29]. It has also been shown that anti-CD20 monoclonal antibodies serve as an effective treatment option for disease modification (see section 1.1.3). Hence, B cells not only play a crucial role for the pathogenesis regarding antigen presentation, but also in its role in the humoral immune system [29]. This is supported by the most prominent gene locus associated with MS identified in genome wide association studies (GWAS). The HLA-DR15 locus encodes for HLA-D proteins, which are major histocompatibility complex (MHC) class II molecules. These are expressed, inter alia, on B cells and other antigen presenting cells [29, 31, 32]. Besides HLA-DR15 there are more than 150 single nucleotide polymorphisms associated with MS found in GWAS [1, 31]. Although most of them have small effect sizes compared to HLA-DR15 [31, 32]. In twin studies, a concordance of 15 % to 25 % was found depending on the country [31–34]. Thus, simple causal relationship between genes and the onset of MS are highly unlikely [19]. It has also been hypothesized that there might be a different genetic background for RRMS compared to PPMS [32].

There is a general consent that the onset of MS cannot solely be explained by genetics, but instead by an interaction of genes and environmental factors [35]. Various environmental factors have been discussed, but only few are consistent throughout literature. For example, Belbasis et al. conducted a review of 44 environmental risk factors like comorbidity, vaccina-

tions, surgeries, traumatic events, accidents, biochemical or musculoskeletal factors, infections, and exposure to environmental agents. Only cigarette smoking, infectious mononucleosis, and IgG seropositivity to Epstein-Barr virus (EBV) showed homogeneous results with a meaningful association with MS [36]. Others argue that vitamin D deficiency is also an important risk factor [32, 37, 38]. Olsson et al. reported that obesity during adolescence might play a role in the onset of MS as well, which might be caused by interacting with HLA risk genes [38]. Another hint might be the different incidence regarding the female-to-male ratio, which changed over the years [3]. This might be caused by changes in western female lifestyle, i.e. in work, cigarette smoking, obesity, birth control, and later childbirth [19]. It is argued that especially cigarette smoking might account for up to 40 % of the increased incidence in females [39]. In comparison to genetic predisposition, these environmental factors are modifiable and thus outstandingly important in regards to prophylaxis, which might be most effective during adolescence [32, 37].

1.1.3 Diagnosis

The current valid criteria for the diagnosis of MS are the 2017 revised McDonald criteria, which contain clinical and paraclinical criteria for the evaluation of dissemination in space and time [40, 41]. The evaluation of clinical symptoms are complemented by MRI and oligoclonal bands in the cerebrospinal fluid (CSF). Dissemination in *space* means lesions in different regions of the CNS diagnosed clinical or by MRI (2 or more lesions located infratentorial, juxtacortical, cortical, periventricular or in the spinal cord diagnosed by T2-hyperintense MRI lesions). Dissemination in *time* describes new lesions over multiple time points, which can also be indicated by MRI, clinical attacks or oligoclonal bands [41]. Oligoclonal bands are a biomarker for chronic inflammation [29].

More precisely, the diagnosis criteria for RRMS state that no additional data is needed if there are at least two clinical attacks with one objective clinical evidence and with history suggestive of a previous attack [40]. If the patient has two or more clinical relapses but only one objective clinical lesion, dissemination in space must be demonstrated additionally. If only one clinical attack is present but at least two objective clinical lesions were found, either dissemination in time or CSF-specific oligoclonal bands have to be present. With only one attack and one objective clinical lesion, dissemination in space and dissemination in time or oligoclonal bands have to be found [40]. To diagnose a progressive disease course the disability progression must have continued over at least one year independent of clinical relapses. Additionally, at least two of the following criteria must be present: one or more T2-hyperintense

lesions at least once either periventricular, cortical, juxtacortical or infratentorial; at least two T2-hypertense lesions in the spinal cord; oligoclonal bands in the CSF [41]. Before making the diagnosis of MS it is important that all differential diagnoses were ruled out [42]. The most relevant alternate diagnoses with a relapsing-remitting course are neuromyelitis optica spectrum disorders, neurosarcoidosis, CNS vasculitis, Susac's syndrome, CADASIL, connective tissue disorders (e.g., systemic lupus erythematosus or Sjögren's syndrome), Behçet's disease, CLIPPERS, and Leber's hereditary optic neuropathy [42]. For a progressive disease course, HTLV1-associated myelopathy, dural arteriovenous fistula, nutritional myelopathy (e.g., vitamin B12 deficiency), primary lateral sclerosis, leukodystrophies, hereditary spastic paraplegia, and spinocerebellar ataxias have to be considered [42].

The 2017 revision of the criteria for clinically isolated syndrome changed in three notable aspects compared to the 2010 revised McDonald criteria [40]. For PwCIS, demonstration of dissemination in space, oligoclonal bands now allow the diagnosis of MS. Also symptomatic lesions can be used for dissemination in either space or time for patients with supra- and infratentorial lesions or spinal cord syndrome. Lastly, the revised criteria offer the option of using cortical lesions as proof for a dissemination in space [40]. For progressive disease courses, the updated criteria includes the removal of the differentiation between symptomatic and asymptomatic MRI lesions and now allows to use cortical lesions for diagnosis [40]. In comparison to the 2010 criteria, the 2017 revised criteria showed a higher sensitivity (0.68-0.83 vs. 0.36-0.66), lower specificity (0.39-0.61 vs. 0.60-0.85), and comparable area under the curve (AUC) (0.61 vs. 0.63) in adults [43, 44]. Furthermore, more diagnoses could be made at baseline with the new criteria [43, 44]. For children, comparable results were found for sensitivity (0.83-0.84 vs. 0.46-0.49) and specificity (0.73-0.92 vs. 0.95-0.97), whereas the accuracy was increased for the new criteria (0.87 vs. 0.67) [45, 46]. Note that the range of most performance estimates is large between studies. The positive and negative predictive values are not reported by any of the studies.

1.1.4 Treatment

The treatment of MS consists of three aspects: reduction of (acute) relapses, modification of future disease activity and progression, and symptomatic therapy. The available DMTs either suppress or modify the immune system [47]. Depending on the disease course and whether the patient has active or highly active MS, different treatments are recommended. The absolute relapse reduction varies between 30 % and 70 % depending on the drug [47]. In progressive forms, the disease progression can be reduced by approximately 20 % [48, 49]. A cure for

multiple sclerosis has yet to be found. Note that neither of the DMTs are evaluated for the elderly population [24]. The symptomatic treatment is most commonly used to treat spasticity, pain, fatigue, cognitive impairment or issues with the bladder, bowel, mood, and sleep [41]. Pharmacological and non-pharmacological options are diverse depending on the symptoms and are beyond the scope of this work.

Betaferones and *glatiramer acetate* were the first treatment options for MS [47]. Their effect on reducing relapses is only moderate but being well-tolerated by most patients and long-term safety made them a first line option in the past [47]. Both substances have an anti-inflammatory effect, although the exact mechanism is still largely unknown [41]. Betaferones are applied subcutaneous or intramusculary either every day or less frequent, while glatiramer acetate is applied subcutaneously daily with one to three doses [47]. As a rare serious adverse event, betaferones can cause liver damage, whereas glatiramer acetate might cause skin necrosis [41]. The monoclonal antibody *natalizumab* inhibits $\alpha 4\beta 1$ integrin leading to reduced transmigration of lymphocytes into the CNS [47]. This highly effective drug is applied intravenously or subcutaneously every four weeks. Severe adverse events include progressive multifocal leukoencephalopathy (PML), hypersensitivity, and liver toxicity [41]. *Dimethyl fumarate* and its recently approved alternative diroximel fumarate are anti-inflammatory and cytoprotective drugs, which are applied orally twice a day. Their moderate disease modifying effect is caused by the activation of the nuclear factor 2 pathway and pathways independent of the former [47]. Though usually well-tolerated with only mild symptoms such as bowel irritations, it can rarely lead to severe infections, PML, lymphopenia, and liver damage [41, 47]. *Teriflunomid* inhibits the pyrimidine synthesis and thus reduces the proliferation of activated lymphocytes [41, 47]. It has a modest effect on the relapse frequency and is applied as a daily oral dose causing headache, diarrhea, nausea, and alopecia. Serious adverse events for Teriflunomid include hepatotoxic and teratogenic effects [41].

The highly effective substances *ocrelizumab*, *rituximab*, and *ofatumumab* are monoclonal anti-CD20 antibodies, which lead to the depletion of CD-20 expressing B cells [41, 47]. The disease modifying effect of ocrelizumab doses every 24 months for relapsing-remitting as well as progressive multiple sclerosis is well-established [47, 49, 50]. Ofatumumab on the other hand is an effective alternative administered monthly, which was only recently in 2021 authorized by the European Medicines Agency (EMA) [51]. While the prescription of rituximab is still off label for PwMS, a recent retrospective analysis as well as a randomized controlled trial showed superior effect compared to betaferone, glatiramer acetate, dimethyl fumarate, fingolimod, or natalizumab [47, 52, 53]. Rare serious adverse events for anti-CD20 antibodies

include Hepatitis B reactivation. The monoclonal anti-CD52 antibody *alemtuzumab* is reserved to severe treatment refractory cases due to severe side effects. The type II topoisomerase inhibitor *mitoxantrone*, though highly effective, is not recommended anymore due to severe toxicities and is thus not further described [47].

Fingolimod, *siponimod*, *ozanimod*, and *ponesimod* are selective S1P-inhibitors, which are applied orally once a day [48, 54, 55]. The S1P receptor modulation leads to a decreased migration of lymphocytes out of the lymphatic nodes and hence to less lymphocytes in the CNS [47]. Ozanimod was only recently authorized by the EMA in 2020 and might supersede fingolimod in the future with promising results in phase III studies providing better safety and tolerability in comparison to fingolimod [56, 57]. Rare but serious adverse effects for fingolimod, siponimod, ozanimod, and ponesimod are bradycardia, heart block, respiratory effects, macular edema, and hepatotoxicity [41]. Additionally, fingolimod shows an increased risk for PML, infections, and posterior reversible encephalopathy syndrome (PRES) [41]. The purine analogous *cladribin* interferes with the DNA- and RNA-synthesis, which leads to an interrupted cell division of lymphocytes. Cladribin is also applied orally 4-5 days over a 2-week treatment course per year for two years [47]. Fingolimod, siponimod, ozanimod, and cladribin have a more moderate effect on disease modification compared to the before mentioned immunsuppressive DMTs [47].

Treatment recommendations. Acute relapses are treated with glucocorticoids. For RRMS, treatment decision depends on disease activity, MRI findings, comorbidities, individual preferences, and family planning [47, 58]. For disease modification, there has been a general paradigm shift to highly efficient DMTs right in the beginning of treatment depending on disease activity [41, 47, 59, 60]. Other promising treatment approaches like mesenchymal stem cells are under investigation [61].

The treatment recommendations differ for progressive forms. In patients with SPMS and disease activity, siponimod is considered first-line option, alternative treatments are anti-CD20 antibodies [47, 48]. Other neuroprotective drugs showed no effect on the progression of MS [62]. A promising substance for patients with SPMS and relapses is tolebrutinib, which is currently under investigation [63]. For patients with PPMS, ocrelizumab is as of today the only option with good evidence reducing the progression up to 25 % compared to placebo [49]. Early and consistent use of ocrelizumab seems to have the best effect on disease progression [64].

1.1.5 Relevance of infections

Practical relevance. Infections are more frequent in PwMS compared to patients without MS (IRR = 1.25-1.76) [15]. Although most infections are mild, the rate of severe infections is considered to be between 0.2 % and 2.6 % [65, 66]. More importantly, systemic infections can lead to exacerbation and relapses [16, 65, 67–69]. Beyond systemic infections, infections of the upper respiratory tract, gastrointestinal or urogenital tract infection have also been associated with exacerbation [70]. Of these peripheral infections, upper respiratory infections had the largest association explaining up to 15 % of the variation in relapses [68, 71]. Previous infections 2-5 weeks before a relapse showed an increased risk, which was 1.3 to 2.8 times higher, although no association was found for infections more than 7 weeks prior to the relapse [65, 69]. Steelman assumed auto-reactive T-lymphocytes as one main cause for this association, as they might get triggered by the infection and cause the worsening of MS symptoms afterwards [16]. Note that the distinction between pseudo-exacerbation and a relapse is not always clear, but the worsening symptoms were observed in either case [65]. In addition, PwMS are twice as likely to be hospitalized for infections compared to the general population [72, 73]. In a large exploratory study for the infection status in the United States of America and the United Kingdom, the incidence rate for any infection in PwMS were 22-48 infections per 100 PY making it a very common problem [15]. This resulted in up to 41 % more physician visits and 57 % more infection related prescriptions [72].

Relevant infections. A severe but a rare infectious disease associated with DMTs in PwMS is PML caused by JC virus. Furthermore, severe varicella zoster infection or reactivation has been described to be associated with DMTs [65, 66, 74]. More frequent are upper respiratory tract infections especially caused by viruses of the picornaviridae [16]. These upper respiratory tract infections are acquired around two times per year in PwMS [16]. Other infections relevant to exacerbation are chlamydia pneumoniae, staphylococcus aureus, viruses of the herpesviridae as well as human retrovirus families [16, 70]. Community acquired pneumonia is 3.6 times higher in PwMS [75]. Pneumonia, urinary tract infections, skin and intestinal infections lead to more than twice as many hospitalizations [72]. Lastly, urinary tract infections are especially common in PwMS, which are often caused by neurogenic bladder dysfunction [76].

Risk factors for infections. *Sex* is one of the most important risk factors, with higher infection risk for female patients [15, 77]. The severity of infections might be increased in male patients with a higher frequency of hospital admissions as well as utilization of physicians and

prescriptions [72, 78]. A progressive *disease course* leads to more infection-related hospital admissions and thus might also result in an increased infection risk [78]. The same applies for a longer *disease duration*, which was on average 5.3 years longer, if a patient was admitted to the hospital because of an infection [78]. A higher *EDSS* score also leads to more hospital admissions with a potential for increasing the infection risk itself (median EDSS of 5 vs. 2) [78]. First-generation DMTs like beta-interferons or glatiramer acetates are not associated with a higher infection risk, whereas second-generation DMTs are known to have an increased infection risk [66, 79, 80]. Cladribine or ocrelizumab have been associated with increases of upper respiratory infections of up to 40 % [41]. Luna et al. found only rituximab having an increased risk for serious infections compared with first-generation DMTs, while fingolimod and natalizumab did not [81]. In general, the *treatment duration* can also increase the risk of infections [66]. Of note, in a large Finnish cohort the use of DMTs was associated with reduced infection-related hospitalizations [78].

Correal et al. found that *T-lymphocyte* activation plays an important role in systemic infections and the risk of relapses, which supports Steelman's hypothesis of auto-reactive T cells being responsible for the association between infections and relapses [16, 67]. *Leukocytes* have also proven to be a valuable biomarker for infections [82]. However, the associations between lymphocytes or leukocytes and the self-reported infection frequency could not be replicated in a study that investigated predictive factors for infections in patients with ocrelizumab treatment [77]. When treated with ocrelizumab, higher serum *IgA* and *IgG* had a protective effect for infections, while leukocytes, lymphocytes, age, EDSS score, disease duration, and number of ocrelizumab doses did not have a meaningful association with the frequency of self-reported infections [77]. Note that these results might be biased since a univariate analysis was conducted as a basis to choose the covariates [83].

Seery et al. found older age to have a protective effect for the infection frequency, while Pirttisalo et al. reported infection-related hospital admissions to be higher with increasing age (on average 8.2 years older) [77, 78]. Cigarette *smoking* and *obesity* are known factors for worse outcomes in infectious diseases and might also affect the susceptibility to get infections in general by altering immune pathways [84–87]. Furthermore, having many comorbidities increases the risk of infection-related hospital admissions [78]. Bladder disturbance also plays a major role in vulnerability to urinary tract infections [15, 88]. Chronic lung diseases like COPD or asthma are risk factors for upper respiratory infections [89, 90]. Other chronic diseases with an increased risk for infectious diseases are chronic kidney disease, chronic blood diseases, inflammatory rheumatism, chronic bowel diseases, and diabetes mellitus [e.g., 15, 91–94].

1.2 Risk assessments for infections

Although there has not yet been an approach for risk assessments in neuroimmunology in general, other disciplines have created risk scores to assess the patients' individual risk for infections. Risk assessments in rheumathology are of special interest, because patients are also treated with medication that alters the immune system. Hence, they might have similar prerequisites as PwMS and PwCIS.

Rheumatology. In rheumatology, the so called Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) risk score is the most established risk assessment. Originally, Strangfeld et al. was investigating the time-dependent decrease in serious infections under TNF-inhibition for the German biologics register RABBIT [95]. Only later the model created in the course of the study was used to predict the rate of serious infections per 100 PY as well as the probability to get at least one serious infection within 12 months [96]. The incidence rate for serious infections was 3 per 100 PY. Covariates used in the RABBIT score to predict serious infections are age (IRR = 1.61), functional disability score (IRR = 1.45), chronic lung disease (IRR = 1.69), chronic kidney disease (IRR = 1.55), previous serious infection (IRR = 2.11), number of treatment failures (IRR = 1.56), mean glucocorticoid dose of 7.5-14 mg/day (IRR = 2.13), mean glucocorticoid dose of more than 14 mg/day (IRR = 4.73), and treatment with a TNF-inhibitor (IRR = 1.81) [96]. Based on these results, an easy to use online calculator was developed. Since then, the RABBIT score has been validated on 1557 patients in Greece [97], 605 patients in Argentina [98], and 272 patients in Romania [99]. Furthermore, Pieringer et al. found that a high RABBIT score is associated with more intensive care unit admissions in patients with rheumatoid arthritis [100].

Besides being well-established with an acceptable predictive accuracy, it is unclear how it translates into an absolute risk increase [101]. It has also been criticized that most of the covariates included in the RABBIT score are not modifiable. Hence, even after accurately estimating the risk of infections for a patient, only the medication can be changed for high risk individuals [101]. Another problem is that the functional disability score is evaluated using a lengthy questionnaire making it potentially impractical in clinical decision making [102]. To solve this, Wang et al. developed their own model based on 263 patients. They focused on the estimation of severe infections requiring hospital admission. Included predictors were low lymphocyte count (OR = 4.08), severe infections in the past 3 years (OR = 3.58), Charlson's comorbidity index (OR = 2.69), and the disease activity score of 28 joints (OR = 1.38) [102]. These results might be overly optimistic, since it is only validated on the same patients the

model was developed on and the confidence intervals are notably wide. Additionally, variables were selected based on univariate statistical significance, which is considered a questionable method to select variables for a multivariate model [e.g., 83]. Other studies focused only on the risk for severe infection under a certain treatment like certolizumab pegol [103]. Curtis et al. found among 1224 patients that age over 70 years (HR = 2.18), diabetes mellitus (HR = 1.98), and chronic lung disease (HR = 2.67) were the most important covariates to predict at least one severe infection. The results were compared to the RABBIT score finding only a moderate agreement between the scores [103].

In an approach for risk assessment for systemic lupus erythematosus instead of rheumatoid arthritis, another prediction model has been developed. Segura et al. investigated the most important covariates for a severe infection defined by hospitalization on 209 patients [104]. The best predictors were age older than 46 (HR = 1.12), Latin American ethnicity (HR = 2.40), corticosteroid dose more than 10 mg/day (HR = 1.33), male sex (HR = 1.49), previous hospitalization for systemic lupus erythematosus (HR = 2.73), Katz quality of living index (HR = 1.06), and any previous infection (HR = 2.40).

Other disciplines. Another discipline where risk assessments for infection is very common is surgery [e.g., 105–108]. More precisely surgical site infections are predicted, which are usually defined as superficial or deep wound infections within 30 days after the operation [106]. The discovered covariates important for infections that might be relevant to multiple sclerosis are smoking status, BMI, and chronic lung diseases [105–107].

More recently, the QCovid algorithm to predict severe cases of SARS-CoV-2 infections has been introduced and validated in the United Kingdom [109–111]. The variables included in the QCovid risk score are: age, Townsend deprivation score, BMI, accommodation, ethnicity, chronic kidney disease, learning disability, chemotherapy in the last 12 months, respiratory cancer, radiotherapy in last 6 months, solid organ transplant, prescribed immunosuppressant medication, leukotriene or long-acting beta blockers, regular prednisolone, sickle cell disease, diabetes mellitus, chronic lung diseases, pulmonary hypertension or pulmonary fibrosis, coronary heart disease, stroke, atrial fibrillation, congestive cardiac failure, venous thromboembolism, peripheral vascular disease, congenital heart disease, dementia, Parkinson's disease, epilepsy, rare neurological conditions, cerebral palsy, severe mental illness, osteoporotic fracture, rheumatoid arthritis or systemic lupus erythematosus, cirrhosis of the liver [109–111]. Note that the rheumatological diseases described earlier are included as risks for infections while MS is not. Since the validation cohorts for the QCovid algorithms were only within coun-

tries in the United Kingdom, it might not be applicable to other countries.

1.3 Objectives

Primary objective: The main aim of this study was the exploratory investigation of potential predictors of the frequency of upper respiratory tract infections and urinary tract infections in PwMS and PwCIS. It was expected that female sex, progressive disease course, higher EDSS, lower lymphocytes, leukocytes and immunoglobulins, longer disease and treatment duration, older age, higher BMI, usage of DMTs, diabetes mellitus, bladder dysfunction, chronic lung disease, and other chronic diseases are associated with a higher risk for infections.

Secondary objectives: Furthermore, the information which was gained from the stepwise data exploration was used (a) to create and evaluate a model to predict the frequency of upper respiratory and urinary tract infections in different samples and (b) to develop a preliminary risk score as a future guidance for clinical decision making.

2 Material and methods

2.1 Study design

Design. This retrospective, cross-sectional, and multi-center study surveyed 389 PwMS or PwCIS about their infection history between March 2020 and March 2022. From the total of 389 participants, 297 patients are treated at the MS clinic of the Department of Neurology of the Medical University of Innsbruck and 92 patients are treated at the neurological outpatient clinic of the Helsinki University. The infection history was gathered with a questionnaire. At the site in Innsbruck the patients were surveyed by two examiners during a routine visit. At the site in Helsinki the questionnaire was sent to patients by post to fill out by themselves. Follow-up calls were made in Helsinki for those who did not reply by post. Inclusion criteria were the diagnosis of either MS or CIS, age $\geq$ 18 years, and a signed informed consent. In Helsinki the patients were matched to the Innsbruck sample by age, EDSS, and disease course with propensity score matching using a caliper of 0.1. For the laboratory values the patients most recent value was used.

Outcome and potential predictors. The outcome was the frequency of upper respiratory and urinary tract infections within the span of two years. Upper respiratory infections included sinusitis, otitis media, pharyngitis, laryngitis, tonsillitis, bronchitis, pneumonia, and pleurisy. Urinary tract infections also covered cases of pyelonephritis. The sum of these frequencies was the dependent variable for all analyses throughout this work. Two separate models were used for variable selection. Model A contains covariates, which might but are not necessarily proven to have a meaningful association with infection frequency. Model B contains only variables based on previous literature. If variables from model A were shown to have a meaningful association, they would be included in model B. Hence, model A can be seen as an exploratory model, which is used to potentially complement model B.

Model A. The potential predictors in model A were age, IgG (mg/dl), IgA (mg/dl), IgM (mg/dl), pack years, body mass index (BMI), disease duration, treatment duration, diabetes mellitus, and other chronic diseases associated with a higher risk of infections. The latter is comprised of chronic kidney diseases, chronic blood diseases, inflammatory rheumatism, chronic liver diseases, and chronic bowel diseases.

Model B. Covariates in model B included sex, EDSS, immunsuppressive medication, immun-

modulative medication, treatment duration, lymphocyte count, leukocyte count, bladder disturbance, chronic lung disease, and disease course. The medication categorized as immunosuppressive treatments were fingolimod (Gilenya®), siponimod (Mayzent®), ozanimod (Zeposia®), ocrelizumab (Ocrevus®), rituximab (MabThera®), alemtuzumab (Lemtrada®), and cladribin (Mavencad®). The immunmodulatory treatments were teriflunomid (Aubagio®), betaferons (Avonex®, Rebif®, Plegidry®), glatiramer acetat (Copaxone®), dimethyl fumarate (Tecfidera®), intravenous immunoglobulin (IVIg), natalizumab (Tysabri®), and tolebrutinib.

Questionnaire. The questionnaire surveyed the infection history, chronic diseases, and other questions associated with infections. The questionnaire was translated from German to Finnish and Swedish, since Finland is bilingual. Note that only the German and Finnish questionnaires are included in the appendix, since the Swedish version is structurally equivalent to the Finnish one. Each upper respiratory tract and urinary tract infection was asked separately. For every of these questions, the frequency and whether the duration was more than four weeks was collected. Furthermore, separate questions for every chronic disease were used. The current smoking status and pack years were also surveyed. Other questions were not directly used in the frame of this study, but can be found in the appendix.

Ethical issues. The study was approved by the ethics committees of the Medical University Innsbruck (Nr.: 1330/2019). The ethics committee from the University Helsinki did not require an additional approval. The data was stored pseudo-anonymously and separated from the unique patient identifier. Only the person directly responsible for this study had access to the data. The study was conducted in accordance with the TRIPOD guidelines [112].

2.2 Statistical analysis

The primary endpoint was identification of the covariates associated with infections. Hence, the frequency of upper respiratory and urinary tract infections served as the outcome. As described in section 2.1, two different models were analyzed using stepwise regression with backward elimination for variable selection. As a link function both Poisson distribution and negative binomial distribution were fitted. The distribution with the better fit was used for the final model. Missing values were removed in the frame of a complete-case analysis. The sample from Innsbruck was split into a train (70 %) and test (30 %) dataset.

First, variable selection was applied on model A with the covariates age, IgG (mg/dl), IgA (mg/dl), IgM (mg/dl), pack years, BMI, disease duration, treatment duration, diabetes mel-

litus, and other chronic diseases associated with a higher risk of infections. Depending on the results, the most important variables would have been added to Model B. The covariates in model B were sex, EDSS, immunosuppressive medication, immunomodulative medication, treatment duration, lymphocyte count, leukocyte count, bladder disturbance, chronic lung disease, and disease course (CIS or RRMS vs. SPMS or PPMS). Both variable selections were applied on the train data set to fit the model. The Akaike information criterion (AIC), pseudo R^2, McFadden's adjusted pseudo R^2, and χ^2 goodness of fit test were used as criteria for model fit. All metric variables were standardized. The β-coefficients are reported as incidence rate ratio (IRR). As a sensitivity analysis for the variable selection process 200 bootstrap samples were drawn from the whole Innsbruck sample (train and test set) with replacement for model A and B. Thus, the risk of a biased selection due to data splitting was minimized.

The stepwise model resulting from fitting model B was used to predict the frequency of infection on the patients from the test data set from Innsbruck. To validate whether the prediction model can be generalized and thus predict the amount of infection in different populations, it was also tested on patients from the test data set in Helsinki. For predictive accuracy, the performance measures root mean square error (RMSE) and mean absolute error (MAE) were used. As a sensitivity analysis, 5 fold cross-validation is repeated a thousand times on the complete Innsbruck data set (train and test set). Hence, the RMSE and MAE were calculated five thousand times, providing estimates independent from data splitting. Finally, the coefficients used to predict the frequencies of infections with model B were used to create a risk score, to assess the amount of infections of future patients. All statistical analyses were conducted in R 4.2.0 or higher with the packages MASS, boot, and bootStepAIC [113–116].

2.3 Sample size considerations

A common approach to approximate the sample size for an unbiased estimation in stepwise variable selection models is to have at least 15 events per variable (EPV) [117]. Previous research found 22-48 events per 100 PY for any infection (including upper respiratory and urinary tract infections) in PwMS and PwCIS in a large register study from the US and UK [15]. Hence, 35 infections per 100 PY were assumed to be found in this study, which corresponds to 210 events in 600 PY. For an observation time of two years per patient, this results in a sample size of at least 300 patients, allowing for robust estimates with up to 14 covariates per model. Although a maximum amount of 10 predictors was chosen in this study, to avoid potential problems with convergence in the frame of variable selection.

3 Results

3.1 Patient characteristics

The flow of participants is shown in Figure 3.1. All missing values were due to missing leukocyte values or leukocytes with a standard deviation larger than 4. The latter was true for one person. Of the 92 patients answering the questionnaire in Helsinki, 14 did not return their in-

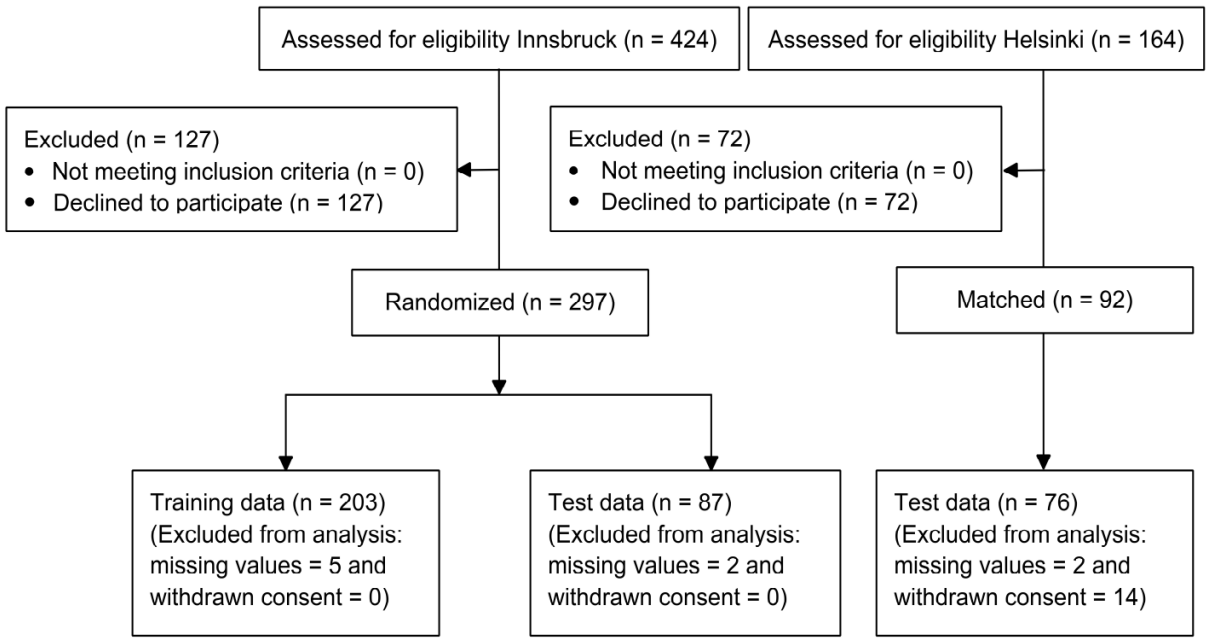

Figure 3.1: Flow of participants in accordance with the TRIPOD guidelines.

formed consent form and thus had to be excluded from the study. The baseline characteristics are shown in Table 3.1. The only notable difference between the three cohorts is the frequency of immunosuppressive and immunomodulative medication, which were more frequent in the Helsinki sample. The remainder of the independent variables were similar throughout the groups. The dependent variable was the summed frequency of upper respiratory tract and urinary tract infections. The distribution of the infection frequency in Innsbruck within the train data set (mean = 3.71, median = 2, maximum = 42, SD = 5.93) was similar to the distribution from the test data set (mean = 3.30, median = 2, maximum = 40, SD = 6.27). In the Helsinki sample, infection frequency was generally lower and contained less outliers (mean = 1.68, median = 1, maximum = 18, SD = 2.78). The incidence rate of upper respiratory infections was 35.71 per 100 PY in the Innsbruck train sample, 33.33 per 100 PY in the Innsbruck test sample, and 28.95 per 100 PY in Helsinki.

Table 3.1: Baseline characteristics of the patients.

	Innsbruck sample		Helsinki sample
	Train data	Test data	
N (with missing values)	203 (208)	87 (89)	76 (78)
Female, n (%)	154 (75.9)	62 (71.3)	53 (69.7)
Age (years), median (IQR)	46 (37, 55)	44 (35, 53)	47 (39, 52)
EDSS, median (IQR)	2 (1, 3.75)	1.5 (1, 2.5)	3 (1.5, 6.5)
SPMS or PPMS, n (%)	40 (19.7)	9 (10.3)	15 (19.7)
BMI, median (IQR)	24 (21, 27)	24 (21, 28)	26 (23, 30)
Pack years, median (IQR)	0.3 (0, 10)	3.1 (0, 10.4)	0 (0, 10.8)
Disease duration, median (IQR)	12 (6, 18.8)	10.5 (5, 18)	11.5 (5, 15.2)
Treatment duration, median (IQR)	2 (0, 5)	2 (0, 4)	5 (3, 9)
Bladder disturbance, n (%)	58 (28.6)	17 (19.5)	18 (23.7)
Chronic lung disease, n (%)	9 (4.4)	3 (3.4)	8 (10.5)
Diabetes mellitus, n (%)	6 (3.0)	3 (3.4)	1 (1.3)
IgA (mg/dl), median (IQR)	169 (122, 229)	162 (122, 240)	*NA*
IgG (mg/dl), median (IQR)	950 (824, 1130)	947 (794, 1140)	*NA*
IgM (mg/dl), median (IQR)	102 (69, 140)	110 (67, 158)	*NA*
Leukocyte (E9/L), median (IQR)	6.7 (5.4, 7.9)	6.6 (5.4, 8.4)	6.1 (5.1, 8.0)
Lymphocyte (E9/L), median (IQR)	1.8 (1.3, 2.3)	1.7 (1.3, 2.3)	1.5 (1.2, 2.0)
Immunosuppressive medication, n (%)	46 (22.7)	23 (26.4)	25 (32.9)
Immunomodulative medication, n (%)	79 (38.9)	32 (36.8)	35 (46.7)

IQR: Interquartile range, NA: not available

3.2 Variable selection

For model A, only IgA and IgG were selected as relevant, with IgA having a positive and IgM having a negative association with the frequency of infections. Since these two variables were not available in the Helsinki test data set, they were not included in model B. The stepwise negative binomial regression for model B selected sex, chronic lung disease, disease course, leukocytes and bladder disturbance as the variables with the largest association with the frequency of infection. Table 3.2 shows the incidence rate ratio (IRR) with 97.5 % confidence intervals, standard error and the test statistic with its corresponding p-value. Apart from the negative binomial distribution, the data was also modeled using a Poisson distribution for count data. The Poisson distribution showed a large overdispersion, which led to using the negative

Table 3.2: Stepwise negative binomial regression model with only the selected variables.

	IRR	$CI_{2.5\%}$	$CI_{97.5\%}$	SE	z-value	p-value
Intercept	1.27	0.82	1.98	0.21	1.10	0.270
Sex (female)	2.51	1.58	3.95	0.23	4.03	< 0.001
Chronic lung disease	1.86	0.87	4.64	0.42	1.48	0.140
Disease course (SPMS/PPMS)	1.50	0.94	2.44	0.24	1.66	0.097
Leukocytes (z-standardized)	1.31	1.00	1.73	0.14	1.97	0.049
Bladder disturbance	1.58	1.04	2.43	0.21	2.12	0.034

IRR: incidence rate ratio, CI: confidence interval, SE: standard error

binomial model instead. Table 3.3 shows the model fit of the two complete models using all variables with Poisson and negative binomial distribution in comparison to the stepwise model. Since the AIC was the lowest in the stepwise model it can be considered the best of those

Table 3.3: Comparison of all three models based on the Innsbruck training data with different model fit indices.

Model	logLik	AIC	p-value	R^2	R^2_{adj}
Poisson	-742.8	1506	< 0.001	0.19	0.138
Negative binomial	-467.1	956	0.099	0.19	0.038
Stepwise negative binomial	-467.8	950	0.140	0.19	0.036

logLik: log-likelihood, AIC: Akaike information criterion

three options. The χ^2 test statistic for the goodness of fit implicated that both negative binomial models had a valid fit. Both the pseudo R^2 as well as McFadden's pseudo R^2_{adj} suggested that there are most likely more unmeasured variables involved, which explain the variation in infection frequencies. The graphical evaluation of the residuals did not show any meaningful violation of the assumption of normality of the residuals (see Figure A.1 in the appendix).

Sensitivity analysis. In Table 3.4 the variables from model A are illustrated. Column two represents the amount to which each variable was selected during the two hundred bootstraps, whereas column three gives the information on whether the resulting β-coefficient was positive in all cases. In 100 % of the cases IgA had a positive and IgG a negative association with the frequency of infections. Table 3.5 shows consistent positive association of sex, bladder disturbance, chronic lung disease, leukocytes, and disease course, while immunosuppressive medication reduced the amount of infections.

Table 3.4: Bootstrap with 200 samples of variable selection for model A.

Variable	Selected (%)	Positive Coefficient (%)
IgA	91	100
IgG	90	0
IgM	45	100
Chronic disease other	44	47
Pack years	42	98
BMI	28	74
Disease duration	26	91
Diabetes mellitus	22	47
Age	22	59
Treatment duration	20	51

Table 3.5: Bootstrap with 200 samples of variable selection for model B.

Variable	Selected (%)	Positive Coefficient (%)
Sex	100	100
Bladder disturbance	93	100
Chronic lung disease	74	99
Leukocytes	58	98
Immunosuppressive medication	55	0
Disease course	51	99
Immunomodulative medication	28	33
EDSS	24	18
Lymphocytes	24	58

Note. All variables selected by the stepwise regression model before are written in bold face.

3.3 Prediction of the frequency of infections

The stepwise procedure applied in the previous section resulted in a model with the covariates sex, chronic lung disease, disease course, leukocytes, and bladder disturbance. This negative binomial model was used to predict the frequency of infections in the test data set from Innsbruck (n = 87) as well as the test data set from Helsinki (n = 76). In figure 3.2, the prediction results are shown as the median infection frequency within two years by the deciles of the expected infection frequency of the training data. This means that the categories on the x-axis are based on the prediction for the training data set (n = 203). The first category con-

tains all infections < 1.89 (n = 129), the second < 2.08 (n = 68), the third < 2.68 (n = 44), the fourth < 2.98 (n = 36), the fifths < 3.18 (n = 39), the sixths < 3.57 (n = 39), the sevenths < 4.12 (n = 48), the eighths < 5.02 (n = 46), the ninth < 7.14 (n = 49), and the tenths decile everything above (n = 41). Each color of the bars corresponds to a different data set. The dark blue

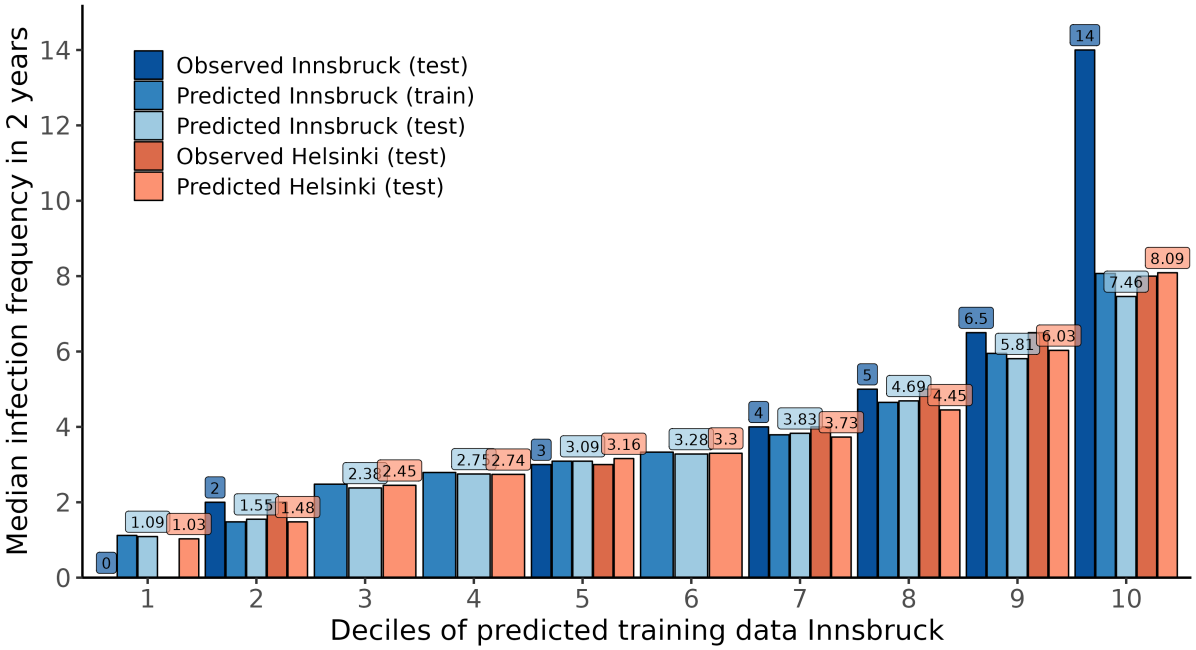

Figure 3.2: Median frequency of infection within 2 years by deciles of the predicted training data from Innsbruck shown for observed and predicted frequencies for Innsbruck and Helsinki data set.

and the dark red are the median observed infection frequencies from Innsbruck and Helsinki respectively. The lighter colors are the median predicted infection frequencies based on the prediction model. For example, the second decile included 68 patients, who have a median infection frequency in two years of between 1.89 and 2.08. The observed frequency for both test data sets from Innsbruck and Helsinki was a median of 2. The expected, i.e. predicted, median frequency of infection in the second decile was 1.55 and 1.69 in Innsbruck and Helsinki. The individual comparison of all patients for the observed and predicted infection frequency is illustrated in Figure A.2 in the appendix.

In Figure 3.3, the probability density distributions of the observed and predicted infections are shown for each sample. The prediction models systematically overestimated the frequency of infections. Furthermore, there were no outliers in the expected samples, but also no zero values (i.e. no infection within 2 years).

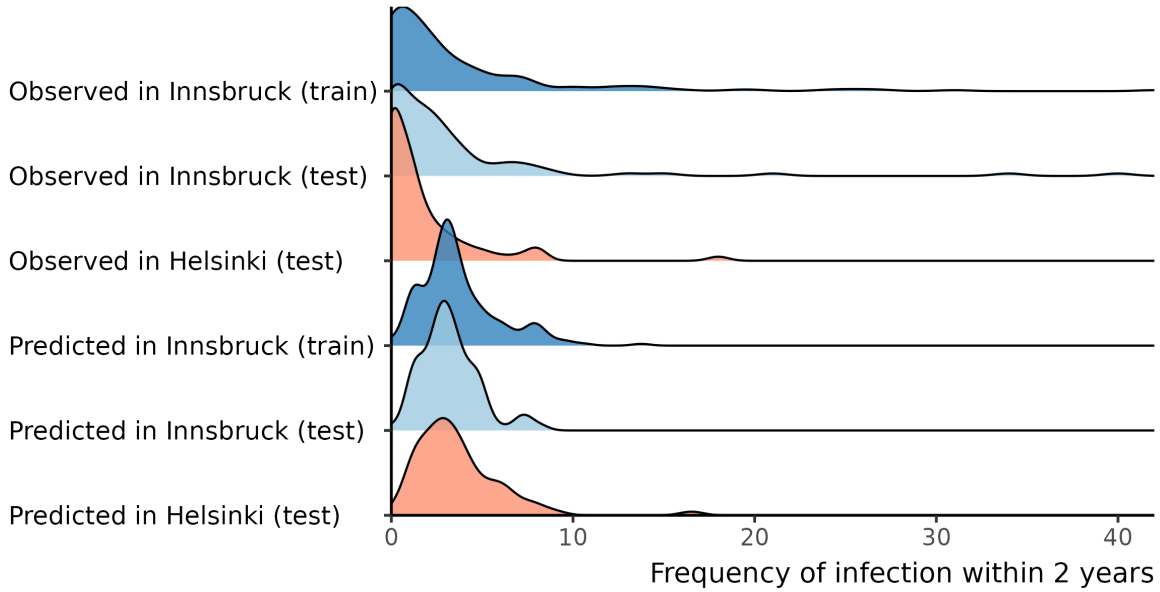

Figure 3.3: Density distributions of the frequency of infection within 2 years.

Predictive accuracy. Predictive performance measures are shown in 3.6. The mean absolute error (MAE) is the average amount by which the estimation deviated from observed values. Hence, in all samples the prediction of the sum of upper respiratory tract and urinary tract infections was off on average around three infections. The root mean square error (RMSE) is

Table 3.6: Comparison of the predictive performance on different data sets.

Prediction	MAE	RMSE	$RMSE_{SD}$	$RMSE_{IQR}$
Innsbruck train data	3.46	5.53	0.93	1.38
Innsbruck test data	3.18	5.98	0.95	1.99
Helsinki test data	3.04	4.09	1.47	2.05

MAE: mean absolute error, RMSE: root mean square error, IQR: interquartile range

higher in all samples with the Helsinki data set having the smallest difference between MAE and RMSE. The latter measure gives more weight to infrequent extreme values (i.e. more than 15 infection in two years). The larger the difference between MAE and RMSE the more inconsistent the error size. The RMSE divided by the standard deviation or interquartile range as shown in columns four and five of Table 3.6 are corrections for outliers, resulting in more similar and smaller root mean square errors. When removing all outliers with infection frequencies of more than 15 within two years, the MAE for the Innsbruck train sample was 2.31, for Innsbruck test sample 2.03, and for Helsinki test sample 2.19. The corresponding RMSE was 3.13 for Innsbruck train, 2.77 for Innsbruck test, and 2.8 for Helsinki test. Figure 3.4 shows the difference between the observed and predicted infection frequency in four risk groups based on the

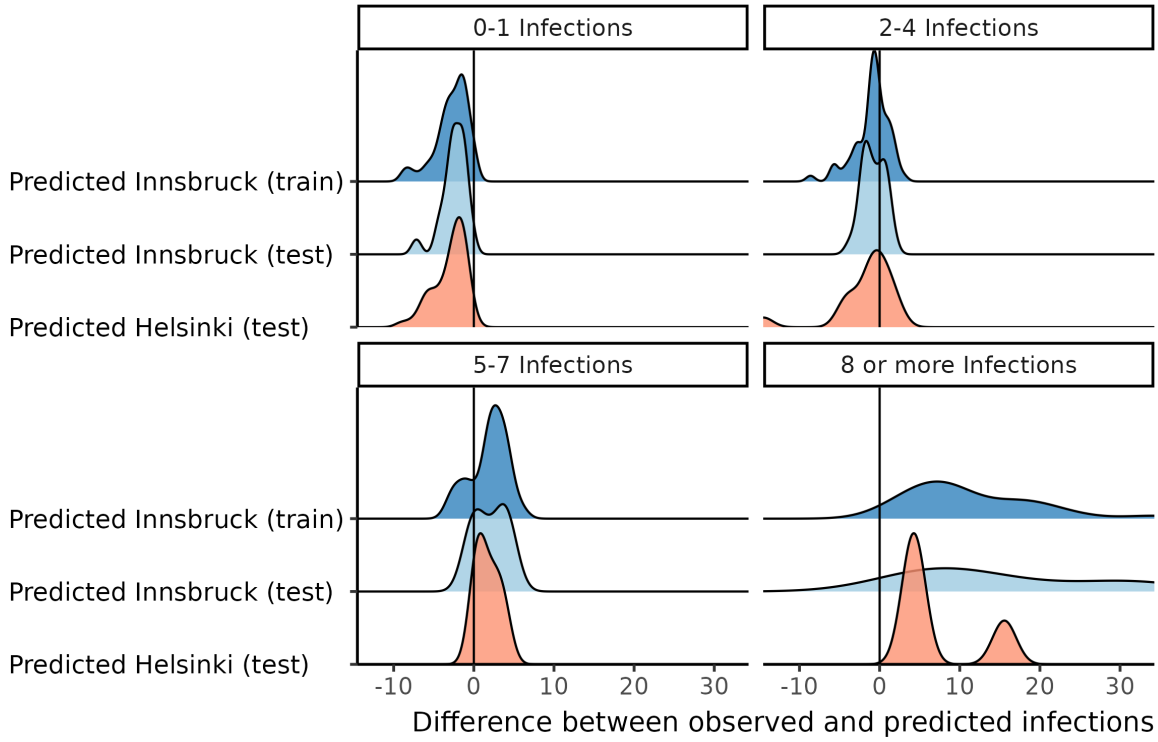

Figure 3.4: Density distributions of the differences between observed and predicted infection frequency within 2 years by four risk groups.

observed values: 0-1 infections (small risk), 2-4 infections (moderate risk), 5-7 infections (high risk), and 8 or more infections (very high risk).

Sensitivity analysis. The 1000 times repeated 5 fold cross validation resulted in a mean MAE of 3.45 (SD = 0.034, SE = 0.001) and a mean RMSE of 5.65 (SD = 0.086, SE = 0.003). These estimates were similar to the values shown in Table 3.6.

3.4 Preliminary risk score

The β-coefficients from the negative binomial model resulting from the stepwise regression in section 3.2 can be used to estimate the frequency of infections for any given new patient. In Table 3.7 the coefficients are shown with an explanation on how to calculate the score. For example, a male patient with a relapsing-remitting MS, chronic lung disease, and leukocytes of 7.9 (E9/L) is expected to have at least 2 (2.55) upper respiratory or urinary tract infections within two years. A female patient with secondary progressive MS, a bladder disturbance, and leukocytes of 5.3 (E9/L) is expected to have at least 6 (6.41) infections within two years. The calculation for the latter example is shown in formula 3.1.

Table 3.7: Preliminary risk score with the β-coefficients to estimate the infection frequency in two years.

Risk factor	Number of upper respiratory tract and urinary tract infections within 2 years	
Intercept	Always add	0.236
Female	If yes add	0.922
Chronic lung disease	If yes add	0.618
SPMS or PPMS	If yes add	0.402
Leukocytes (E9/L)	(Leukocyte − 7.01) / 2.91	0.270
Bladder disturbance	If yes add	0.457
Pre-calculation	Sum all values	sum
Infection score	Calculate	e^{sum}

$$\exp(0.236 + 1 * 0.922 + 1 * 0.402 + \left(\frac{5.3 - 7.01}{2.91} * 0.270\right) + 1 * 0.457) = 6.413 \qquad (3.1)$$

Formula 3.1: Regression equation for a practical example.

4 Discussion

More than 2.2 million patients are diagnosed with MS worldwide. The early onset around the age of 30 and substantial disabilities lead to an immense burden of disease. High efficacy treatments are now available, but are associated with relevant side effect such as infections. Particular in elderly patients, treatment effects decrease and side effects are more common. To predict the risk of infection would be a valuable tool for a treatment decision. Therefore, this study developed a preliminary risk score based on the most important predictors for the risk of infections. Of the 19 investigated variables only sex, chronic lung disease, disease course, leukocytes, and bladder disturbance were included into the final model. The other potential predictors – namely immunoglobulins, pack years, BMI, disease duration, treatment duration, age, medication, EDSS, lymphocytes, diabetes mellitus, and other chronic diseases associated with an increased risk of infections – did not show a meaningful association with the frequency of infections in this study.

The model predicted on average three infections more or less than the observed, i.e. true, values. The model is not over-fitted on the train data set, because the expected frequencies of the train sample were similar to the test sample from Innsbruck as well as the test sample from Helsinki (in particular after removing the outliers). However, a potential problem is that it is very common for PwMS and PwCIS to have at least one of the covariates female sex, bladder dysfunctions, chronic lung disease, progressive disease course or increased leukocytes (probably due to a current infection at that time). Because of the positive intercept and relatively large β-coefficients, the estimate for infection only rarely equaled zero. In the observed data on the other hand, a significant proportion of patients had no infections within two years (Innsbruck train: 29 %, Innsbruck test: 33 %, Helsinki test: 43 %). The only negative influence can be a 'normal' leukocyte count (i.e. smaller than the mean). A reason for the overestimation of infection risk in low risk patients could be the lack of investigated protective factors in this study. On the other side, for high and very high risk individuals with 5 to 7 respectively 8 or more infections, the infection frequency was underestimated. The underestimation for high risk individuals might be explained by the demographic characteristics of the population. Included patients were relatively young with a low EDSS. The fact that the used performance measures for predictive accuracy are based on the mean, is a reason for the large impact of a few outliers.

More specifically, the prediction model performed well for patients in the second to eighth decile, while the 10 % with the least infections were overestimated and the 20 % with the most infections were underestimated. The IRR for sex of 2.51 was higher than found by Persson et

al., who reported an increased incidence ratio between 1.46 and 1.78 [15]. The IRR for chronic lung disease of 1.86 was comparable to the risk ratio for severe infections of 1.69 and for hospitalizations due to upper respiratory tract infections in patients with moderate COPD with an IRR of 1.98 [89, 96]. The standard error for chronic lung disease was high and its confidence interval wide, because the number of chronic lung diseases within the train sample was only 10 (of 203). The effect of a progressive disease course was smaller with 1.50 than expected based on an univariate IRR for infection-related hospitalizations of 4.68 [78]. There are no comparable previous incidence rates for bladder disturbance, but an increased infection risk is expected [15, 76]. In general, incidence rate ratios are expected to be biased too large due to the stepwise procedure. High leukocytes as a predictor for more infections are counterintuitive. One possible explanation is that some patients had a latent infection at the time of blood sampling. Thus, this covariate might actually be a proxy variable for previous infections, since it is a known useful biomarker for that cause [82]. The same might apply for immunglobulin A, which is typically high after upper respiratory tract infections. Thus, the positive association might be a proxy for a previous or chronic infection. Usually a high IgA should reduce the infection risk in PwMS [77]. In this study, IgG had negative association with infection frequency, which corresponds to the protective effect found in previous research [77]. Another possible explanation for the selection of IgA and IgG by the alternate stepwise regression model is that the other predictors association with the infection frequency was so small that the immunoglobulins were selected despite a potentially negligible effect. The other variables were selected in less than 50 % of the cases, which is most likely merely coincidental. Both sensitivity analyses confirmed the results.

Limitations. The retrospective and self-survey nature of this study might led to over- or underestimation of the actual frequency of infections caused, inter alia, by forgetting. The matched study design is a strength of this study and also a limitation, because it limits the extent of generalization to populations in other countries or age groups. Another limitation is the time frame of the study. During that time, the global SARS-CoV-2 pandemic led to mandatory usage of FFP-2 masks in public and quarantine with flu-like symptoms. Especially the frequency of upper respiratory infections might be inversely affected by the countermeasures against SARS-CoV-2. Furthermore, the study did not have the power to investigate rare severe infections with potential hospitalizations.

Future research. The model should be trained and tested on a large sample size again with-

out variable selection, so the β-coefficients will be unbiased and thus most likely smaller. This might lead to better prediction accuracy for patients with a low infection risk. A large sample would also make it possible to apply a zero-inflated model instead, to model the low risk population more precisely. Furthermore, the influence of DMTs can only be investigated in larger sample sizes. This is of special interest as it gives a modifiable factor for the risk of infections. Particularly patients who are treated with cell-depleting agents are affected, since their risk of upper respiratory infections is increased up to 40 % [41]. Lastly, protective factors for infections should be further investigated before clinical usage of the preliminary risk score, because this study only focused on risk factors. Other potentially important but unmeasured variables might be different comorbidities (e.g., cardiovascular diseases) and previous (severe) infections.

Final remarks. Infections play a critical role in the morbidity and mortality of people with MS or CIS. The most important factors found in this study were female sex, chronic lung disease, secondary or primary progressive disease course, high leukocyte count in peripheral blood, and bladder disturbance. This study provides first insights into an interpretable model for the prediction of infection frequencies.

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6 List of abbreviations

AIC Akaike information criterion. 22, 23, 26

AUC area under the curve. 12

BMI body mass index. 19–22, 31

CADASIL cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. 12

CIS clinically isolated syndrome. 22, 34

CLIPPERS chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. 12

CNS central nervous system. 7, 11–14

COPD chronic obstructive pulmonary disease. 8, 17, 33

CSF cerebrospinal fluid. 11, 12

DALYs disease-adjusted life years. 7

DMTs disease modifying treatments. 7, 13, 15–17, 20, 34

DNA deoxyribonucleic acid. 14

EBV Epstein-Barr virus. 11

EDSS Expanded Disability Status Score. 16, 17, 20–22, 27, 31, 32

EMA European Medicines Agency. 14

FFP-2 filtering face piece 2. 33

GWAS genome wide association studies. 10

HLA human leukocytes antigen. 10, 11

HR hazard ratio. 19

HTLV human T-lymphotropic virus. 12

IgA immunglobulin A. 21, 22, 25–27, 33

IgG immunglobulin G. 21, 22, 25–27, 33

IgM immunglobulin M. 21, 22, 25, 27

IRR incidence rate ratio. 18, 23, 25, 26, 32, 33

JC John Cunningham. 15, 16

MAE mean absolute error. 23, 29, 30, 32

MHC major histocompatibility complex. 10

MRI magnetic resonance imaging. 11, 12

MS multiple sclerosis. 7–16, 30, 31, 34

OR odds ratio. 18

PML progressive multifocal leukoencephalopathy. 13, 14, 16

PPMS primary progressive multiple sclerosis. 11, 15, 22, 26

PRES posterior reversible encephalopathy syndrome. 14

PwCIS people with clinically isolated syndrome. 8, 9, 12, 15, 17, 20, 23, 32

PwMS people with multiple sclerosis. 7–9, 14–17, 20, 23, 31–33

PY patient years. 9, 10, 16, 18, 23, 24

RABBIT Rheumatoid Arthritis Observation of Biologic Therapy. 18, 19

RMSE root mean square error. 23, 29, 30, 32

RNA ribonucleic acid. 14

RRMS relapsing-remitting multiple sclerosis. 7, 11, 15, 22

S1P sphingosine-1-phosphate. 14

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2. 19, 33

SD standard deviation. 24, 30

SE standard error. 30

SPMS secondary progressive multiple sclerosis. 15, 22, 26

TNF tumor necrosis factor. 18

TRIPOD transparent reporting of a multivariable prediction model for individual prognosis or diagnosis. 3, 22, 24

A Appendices

A.1 Supplementary figures

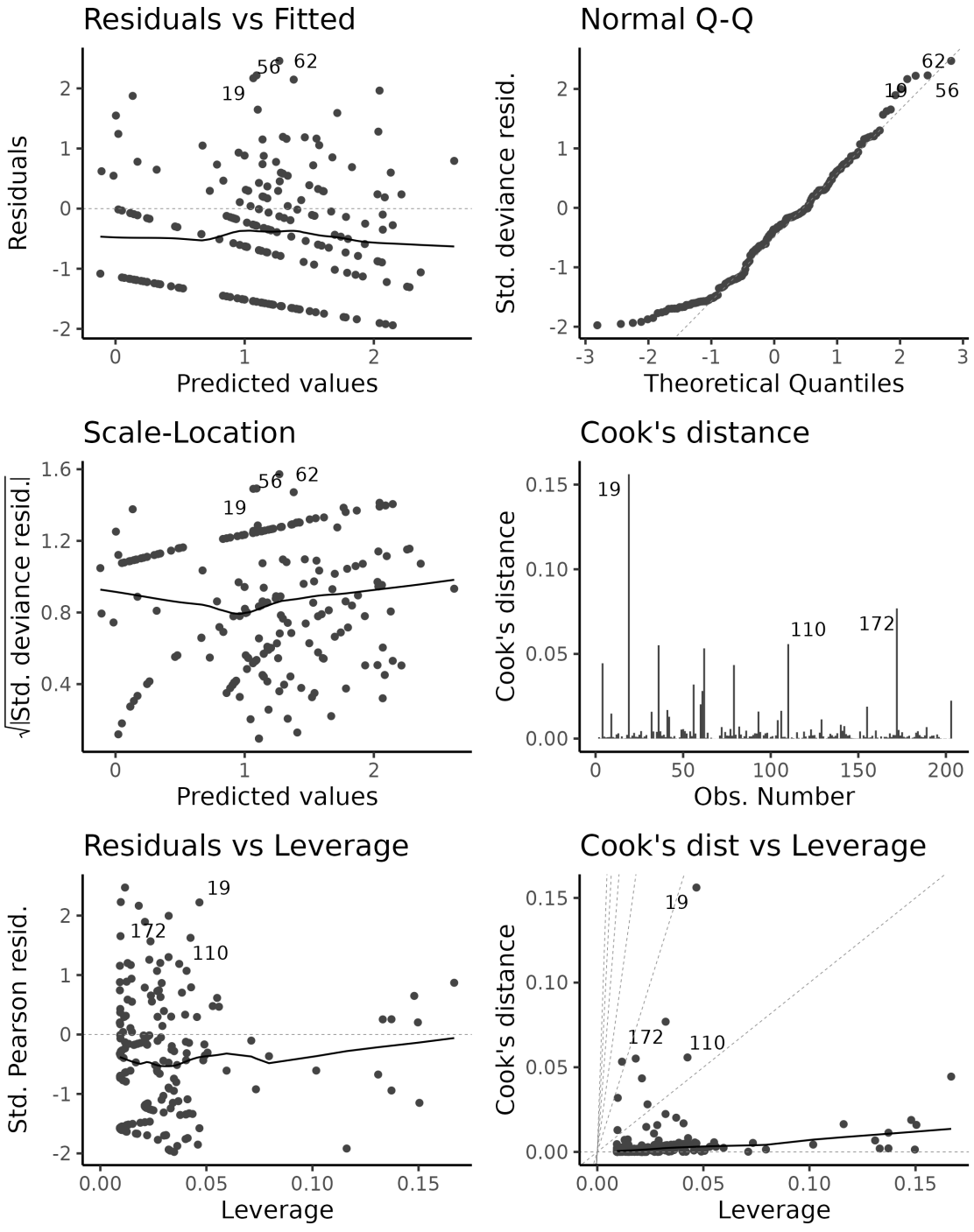

Figure A.1: Illustration of the residuals from the stepwise negative binomial regression model.

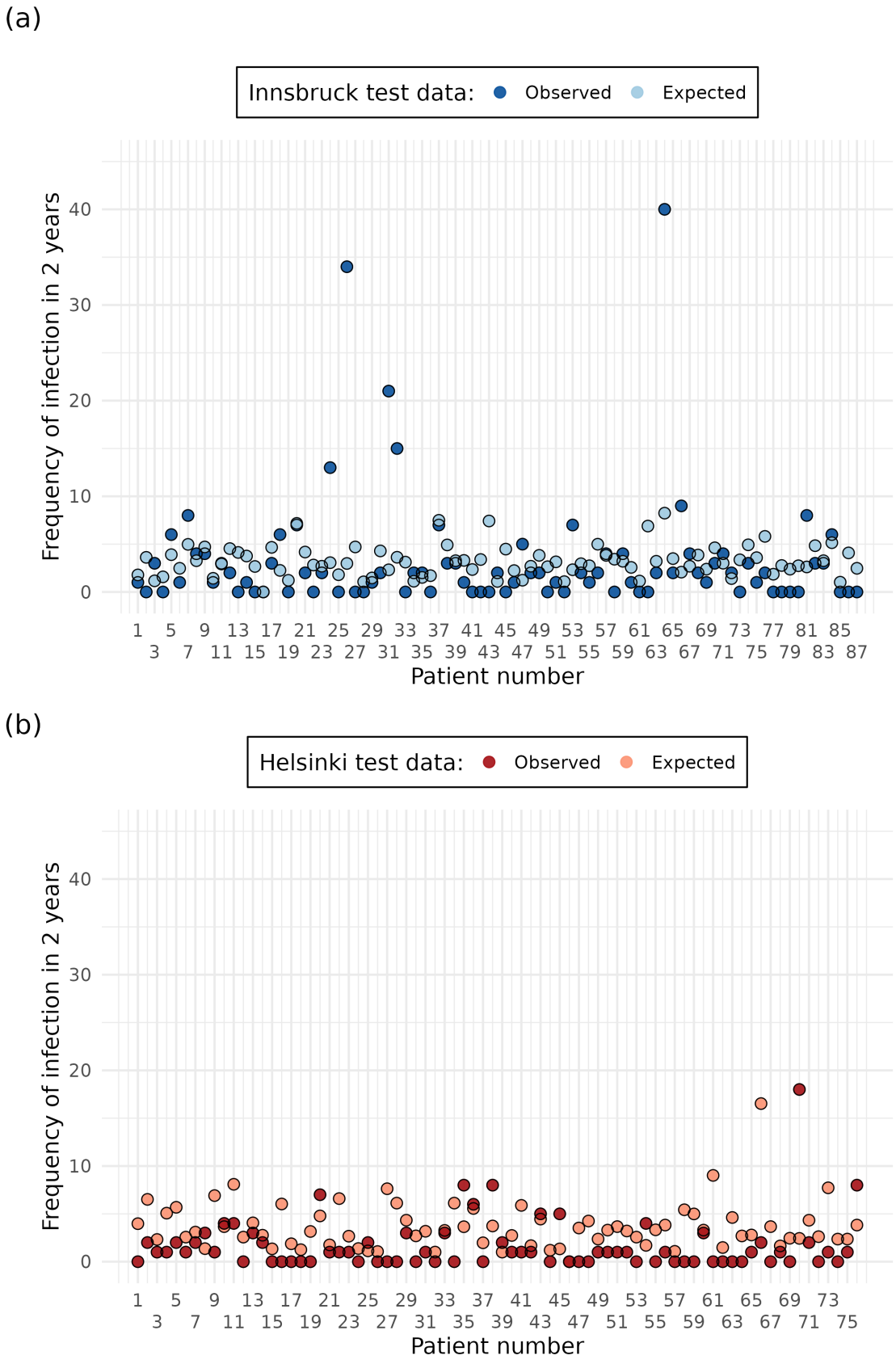

Figure A.2: Frequency of infections within 2 years of every individual patient in (a) Innsbruck and (b) Helsinki.

A.2 Questionnaires

*Impfstatus bei Patient*Innen mit Multiple Sklerose Version 1.1 vom 21.07.2021*

Multiple Sklerose und Infektionen – Case Report Form

Wie häufig litten sie in den letzten 2 Jahren an nachfolgend aufgeführten Atemwegsinfektionskrankheiten? **- Bitte ankreuzen: Nie, 1-3 Mal, häufiger als 3x** **- Bitte kreuzen sie auch die jeweilige Dauer an**					
	Häufigkeit			**Dauer**	
	Nie	**1-3x**	**>3x**	**Unter 4 Wochen**	**Über 4 Wochen**
Nasennebenhöhlenentzündung (Sinusitis)					
Schnupfen					
Mittelohrentzündung					
Rachen- und Kehlkopfentzündung (Heiserkeit)					
Mandelentzündung					
Grippaler Infekt (Fieber, Husten, Gliederschmerzen)					
Bronchitis					
Pneumonie (Lungenentzündung)					
Rippenfellentzündung					
Andere Atemwegsinfektionen, wenn ja welche					

	Nie	**1-3x**	**4-6x**	**>6x**
Wie häufig wurden Ihnen in den letzten 2 Jahren auf Grund eines Atemwegsinfekt Antibiotika verschrieben?				

	Nein	**Ja**
Hatten sie als Erwachsener insgesamt 3 oder mehr schwerwiegende Atemwegsinfekt wie eine schwere Bronchitis oder Lungenentzündung?		
Hatten sie als Erwachsener jemals über 4 Wochen dauernde Atemweginfektionen?		

Wie häufig litten sie in den letzten 2 Jahren an einem Harnwegsinfekt? **- Bitte ankreuzen: Nie, 1-3 Mal, häufiger als 3x** **- Bitte kreuzen sie auch die jeweilige Dauer an**					
	Häufigkeit			**Dauer**	
	Nie	**1-3x**	**>3x**	**Unter 4 Wochen**	**Über 4 Wochen**
Harnwegsinfektion					
Nierenbeckeninfektion					
	Nie	**1-3 Mal**		**4-6 Mal**	**Mehr wie 6 Mal**
Wie häufig wurden Ihnen in den letzten 2 Jahren auf Grund eines Harnwegsinfektion Antibiotika verschrieben?					
Musste das Antibiotika auf Grund einer sogenannten Resistenz gewechselt werden					
	Nein			**Ja**	
Hatten sie als Erwachsener insgesamt 3 oder mehr schwerwiegende Harnwegsinfektionen?					
Hatten sie als Erwachsener jemals über 4 Wochen dauernde Harnwegsinfektionen?					
Haben diese Harnwegsinfektionen zu einem stationären Aufenthalt im Krankenhaus geführt					
Müssen Sie wegen häufiger Harnwegsinfekte eine antibiotische Prophylaxe nehmen?					

Waren Sie wegen einem Infekt in den letzten 24 Monaten im Krankenstand? Bitte ankreuzen bzw ausfüllen		
Nein	**Ja**	**Wie oft?** **-------**

Hatten sie in der Vergangenheit jemals einen der nachfolgenden schwerwiegenden Infektionen?		
	Nein	**Ja**
Blutvergiftung (Sepsis)		
Abzess (eitrige Entzündung) innerer Organe		
Abzess (eitrige Entzündung) Lymphknoten		
Herzklappenentzündung		
Schwere Knochenentzündung (Osteomyelitis)		
Eitrige Gelenksentzündung		
Tuberkulose		
Chronische Leberentzündung (Hepatitis B oder C)		
Hirnhautentzündung (Meningitis)		
Andere schwerwiegende Infektionen (bitte unten beschreiben):		

Wurden sie jemals wegen einem dieser Infekte stationär im Krankenhaus aufgenommen? Bitte ankreuzen bzw. ausfüllen			
Nein	**Ja**	**Wie oft?**	**In welchem Alter das erste Mal?**
		-------	**------**

Wurde bei Ihnen als Erwachsener eine dauerhafte Vergrößerung der Milz, Lymphknoten oder Rachenmandeln (über 6 Monate festgestellt?	
Nein	**Ja**

Wurden bei Ihnen folgende Organe dauerhaft entfernt?		
	Nein	**Ja**
Rachen- oder Gaumenmandeln		
Polypen bzw. andere Nasennebenhöhlen-OP		
Blinddarm		
Milz		
Thymus		
Hatten sie andere Operationen im Bereich der Atemwege, wenn ja welche:		

Haben Sie das Gefühl leicht an Atemwegsinfekten zu erkranken?	
Nein	**Ja**

Wie sehr haben sie das Gefühl durch Atemwegsinfekte in Ihren Aktivitäten beeinträchtigt zu sein?				
Nie	**Selten**	**Ab und zu**	**Häufig**	**Dauerhaft**

Zum Abschluss beantworten Sie bitte noch allgemeine Fragen zu bestimmten chronischen Krankheiten, Lebensstil und demographischen Faktoren:

Leiden Sie an einer der folgenden Krankheiten über 6 Monate (bitte Ja oder Nein ankreuzen)		
	Nein	**Ja**
Blasenentleerungsstörung		
Chronische Raucherlunge (COPD), Lungenemphysem		
Chronisches Asthma		
Chronische Nierenkrankheit		
Chronische Blutkrankheit (zB. Lymphom, Leukämie)		
Entzündliches Rheuma		
Chronische Lebererkrankung (z.B. Vergrößerung, Zirrhose)		
Chronisch entzündliche darmerkrankung (z.B. Colitis ulcerosa, Mb. Crohn)		
Diabetes mellitus		
Ist der Diabetes mellitus Insulin-pflichtig?		
Allergien:		
Neigung zu allergischem Asthma, spastischer Bronchitis		
Heuschnupfen (Pollen)		
Hausstauballergie		
Nahrungsmittelallergie		
Kontaktekzem		
Andere Allergien, wenn ja, welche		

Leiden Sie an einer Tumorerkrankung		
	Nein	**Ja**
Wenn ja welche? Erhalten Sie derzeit diesbezüglich eine Therapie (bitte kurz beschreiben)?		

Leiden Sie an einer anderen chronischen Erkrankung außer der oben genannten bzw. außer einer MS?		
	Nein	**Ja**
Wenn ja welche? Erhalten Sie derzeit diesbezüglich eine Therapie (bitte kurz beschreiben), insbesondere dauerhafte Kortisoneinnahme (über 6 Monate)?		

Rauchen Sie oder haben Sie geraucht?		
Nie	**Früher**	**Aktuell Raucher**
Was rauchen Sie bzw. haben Sie geraucht		
Zigaretten	Pfeife	Zigarren
Wieviel Stück rauchen Sie pro Tag? _____		
Wieviel Jahre haben Sie geraucht bzw rauchen Sie bereits?		

Wieviel Kontakt haben Sie zu Kindern im Kindergarten- oder Volksschulalter?			
Nie	**Selten**	**Wöchentlich**	**Täglich**

Leben Sie in der Stadt oder in einem ländlichen Gebiet?	
Stadt	**Land**

Haushalt	
Anzahl der Personen im Haushalt?	
Anzahl der Kindergarten- oder Schulkinder im Haushalt?	

Was machen Sie beruflich?	
In keinem Arbeitsverhältnis	
Pensioniert	
Student	
Gesundheitsberuf (Arzt, Pflegekraft, etc.)	
Büroarbeit	
Arbeiter	
Andere:	

Wie oft haben Sie <u>beruflich bedingt</u> Kontakt mit anderen Menschen			
Selten (zB Büro alleine)	**Regelmäßig**	**Häufig**	**Ständig** (zB Verkäufer*in)

Beantworten Sie bitte noch Fragen zu Covid-19!

Hatten Sie eine Covid-19 Infektion?	
Ja	**Nein**

Wenn NEIN:

Sind Sie gegen Covid-19 geimpft?	
Ja	**Nein**

Welchen Impfstoff haben Sie erhalten?	
Biontech-Pfizer	
Moderna	
Astra-Zeneca	
Johnson&Johnson	
Andere:	
Datum der Impfung?	
1. Impfung	
2. Impfung (falls zutreffend)	

WENN JA:

Siehe Folgeseite

Erkrankungsverlauf		
Datum der Covid-19 Diagnose		
Datum 1. positive SARS-CoV-2 PCR		
Covid-19 Schweregrad		
Mild Alle Fälle ohne Pneumonie oder milde Pneumonie ohne Erfüllung eines der Kriterien für schweren oder kritischen Verlauf.	**Schwer** Atemnot, Atemfrequenz ≥30/Minute, SpO2 ≤93%, PaO2/FiO2-Ratio <300 und/oder Lungeninfiltrat >50% innerhalb von 24-48h	**Kritisch** Auftreten von respiratorischer Insuffizienz, septischem Schock und/oder Multiorganversagen

Hospitalisierung	
Ja	**Nein**

Mechanische Beatmung	
Ja	**Nein**

Outcome		
	Nein	**Ja**
Keine Beschwerden mehr		
Allgemeinzustand verschlechtert im Vergleich zu vor Covid-19		

Wenn eine Verschlechterung nach Covid-19 besteht, welche Art?			
Physisch		**Wenn ja:**	
		Geruchs/ Geschmacksinn	
		Kurzatmigkeit	
		Reduzierte Kondition	
		Verschlechterung MS Symptome	
Kognitiv			
Psychisch		**Wenn ja:**	
		Depression	
		Angst	
Fatigue			

1.1 Kuinka usein teillä on ollut jokin seuraavista infektioista viimeisen kahden vuoden aikana?

	Esiintymistiheys	Kesto > 4 viikkoa
Sivuontelotulehdus (Sinuiitti)		
Flunssa		
Välikorvatulehdus		
Nielutulehdus ja käheys (Faryngiitti ja laryngiitti)		
Risatulehdus (Tonsilliitti)		
Keuhkoputkentulehdus (Bronkiitti)		
Keuhkokuume (Pneumonia)		
Keuhkopussintulehdus (Pleuriitti)		
Muut hengitystieinfektiot:		
Virtsatieinfektio		
Munuaisaltaan tulehdus (Pyelonefriitti)		

1.2 Kuinka usein teille on määrätty antibiootteja hengitystieinfektioon viimeisen kahden vuoden aikana?

1.3 Onko teillä ollut 3 tai enemmän vakavaa hengitystieinfektiota aikuisena (esim. akuutti keuhkoputkentulehdus tai keuhkokuume)? (Ei, Kyllä)

1.4 Onko teillä koskaan ollut kroonista hengitystieinfektiota, joka olisi kestänyt yli 4 viikkoa? (Ei, Kyllä)

1.5 Kuinka usein olette käyttäneet antibiootteja virtsatieinfektioon?

1.6 Oletteko joutuneet vaihtamaan antibiootteja antibioottiresistenssin takia? (Esiintymistiheys)

1.7 Onko teillä ollut 3 tai enemmän vakavaa virtsatieinfektiota aikuisena? (Ei, Kyllä)

1.8 Onko teillä ollut yli 4 viikkoa kestävää virtsatieinfektiota? (Ei, Kyllä)

1.9 Onko teillä ollut sairaalahoitoa vaativaa virtsatietulehdusta? (Ei, Kyllä)

1.10 Käytättekö usein antibioottiprofylaksia? (Ei, Kyllä)

2.1 Kuinka usein olette olleet sairaslomalla infektion takia viimeisen kahden vuoden aikana?

3.1 Onko teillä ollut jokin seuraavista vakavista infektioista? (Ei, Kyllä)

	Esiintymistiheys	Kesto > 4 viikkoa
Verenmyrkytys (Sepsis)		
Sisäelinten paise		
Imusolmukkeiden paise		

Sydänläppätulehdus (Valvuliitti)		
Luutulehdus (Osteomyeliitti)		
Märkivä niveltulehdus		
Tuberkuloosi		
B- tai C-hepatiitti		
Aivokalvontulehdus (Meningiitti)		
Muut vakavat infektiot:		

3.2 Oletteko koskaan saaneet sairaalahoitoa jonkin yllämainitun vakavan infektion takia? (Ei, Kyllä, Kuinka usein?, Ikä ensimmäisellä kerralla)

4.1 Onko teillä diagnosoitu suurentunut perna, suurentuneet imusolmukkeet tai nielurisat aikuisiässä (yli 6 kk ajan)? (Ei, Kyllä)

4.2 Onko jokin seuraavista elimistä poistettu pysyvästi? (Ei, Kyllä)

Poistettu elin	Kyllä
Kita- tai nielurisat	
Polyyppejä tai muu nenän sivuontelon leikkaus	
Umpilisäke	
Perna	
Kateenkorva	
Muut hengityselinten alueen leikkaukset:	

5.1 Sairastutteko helposti hengitystieinfektioihin? (Ei, Kyllä)

5.2 Kuinka usein hengitystieinfektiot rajoittavat toimintojanne? (Ei koskaan, harvoin, välillä, usein, jatkuvasti)

6.1 Onko teillä tällä hetkellä jokin seuraavista sairauksista (sairaus ollut vähintään 6 kuukautta)?

Krooninen sairaus	Kyllä
Virtsarakon tyhjennyshäiriö	
Keuhkoahtaumatauti (COPD)	
Krooninen astma	
Krooninen munuaissairaus	
Krooninen verisairaus (esim. lymfooma, leukemia)	
Tulehduksellinen reuma	

Krooninen maksasairaus (esim. suurentunut maksa, kirroosi)	
Krooninen suolistosairaus (esim. haavainen paksusuolentulehdus, Crohnin tauti)	
Diabetes mellitus	
Insuliinihoitoinen diabetes mellitus	

7.1 Onko teillä jokin seuraavista allergioista?

Allergia	Kyllä
Taipumus allergiseen astmaan tai spastiseen bronkiittiin	
Siitepölyallergia	
Pölyallergia	
Ruoka-aineallergia	
Allerginen kosketusihottuma	
Muut allergiat:	

8.1 Onko teillä syöpä? (Ei, Kyllä)

8.2 Jos kyllä, niin mikä?

8.3 Jos kyllä, niin saatteko tällä hetkellä syöpähoitoa? (lyhyt kuvaus)

9.1 Onko teillä MS-taudin ja aikaisemmin mainittujen sairauksien lisäksi jokin toinen krooninen sairaus? (Ei, Kyllä)

9.2 Jos kyllä, niin mikä?

9.3 Jos kyllä, niin oletteko yli kuuden kuukauden sisällä saaneet hoitoa kyseiseen sairauteen (erityisesti kortikosteroidit)? (lyhyt kuvaus)

10.1 Tupakoitteko tällä hetkellä tai oletteko tupakoineet aikaisemmin? (Ei koskaan, aikaisemmin, tällä hetkellä)

10.2 Jos kyllä, niin mitä tuotteita poltatte? (savukkeita, piippua, sikareita)

10.3 Jos kyllä, niin kuinka paljon poltatte päivittäin?

10.4 Jos kyllä, niin kuinka kauan olette tupakoineet?

11.1 Kuinka usein olette tekemisissä päiväkoti- tai esikouluikäisten lasten kanssa? (Ei koskaan, harvoin, viikoittain, päivittäin)

11.2 Asutteko kaupungissa vai maaseudulla? (Kaupunki, Maaseutu)

11.3 Kuinka monta henkilöä asuu kotitaloudessanne?

11.4 Kuinka monta päiväkoti- tai esikouluikäistä lasta kotitalouteenne kuuluu?

11.5 Mitä teette työksenne? (Työtön, eläkkeellä, opiskelija, terveydenhuolto (lääkäri, sairaanhoitaja jne.), toimistotyö, muu)

11.6 Kuinka usein olette tekemisissä muiden henkilöiden kanssa työssänne? (Harvoin, säännöllisesti, usein, päivittäin)