

UNIVERSITA' DEGLI STUDI DI PAVIA

FACOLTA' DI INGEGNERIA
DIPARTIMENTO DI INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE

DOTTORATO DI RICERCA IN BIOINGEGNERIA, BIOINFORMATICA E TECNOLOGIE PER LA SALUTE
XXXVIII - 2025

MACHINE LEARNING FOR PREDICTING MULTIPLE SCLEROSIS PROGRESSION USING CLINICAL AND ENVIRONMENTAL DATA

PhD Thesis by
MAHIN VAZIFEHDAN

Advisors:
Prof. Arianna Dagliati
Prof. Riccardo Bellazzi

PhD Program Chair:
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to my parents,

*“There is no one path to success.
You have to find your own way
and embrace the challenges
along the journey.”*

Maryam Mirzakhani



Acknowledgments

This dissertation would not have been possible without the guidance, support, and encouragement of many individuals whose valuable assistance has been instrumental in both the preparation and completion of this work.

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And finally, to Sahar, Nima, Liam, and Levin, thank you for the happiness you bring into my life.

Mahin Vazifehdan
Pavia, October 2025

Abstract (English)

Multiple Sclerosis (MS) has become an increasing focus of research in recent years, driven by its growing prevalence and substantial impact on public health. It is a lifelong, chronic neuroinflammatory disorder that progressively impairs neurological function and often leads to significant disability. Despite therapeutic advances that slow disease activity, MS remains a chronic condition, and identifying the factors that drive disease progression is essential for long-term management and improved quality of life. While clinical and demographic determinants of progression are well established, the role of environmental exposures remains less clearly understood.

This work is conducted within the framework of the *BRAINTEASER* project, which aims to support Artificial Intelligence (AI)-driven care for patients with MS and Amyotrophic Lateral Sclerosis (ALS) by integrating clinical and environmental data across three European countries (Spain, Italy, and Portugal). Within this context, the work investigates the role of environmental exposures, specifically air pollution and weather conditions, in MS progression and prediction, in combination with clinical and demographic information.

The study is organized around three main aims. **Aim 1**, addressed

in Chapter 3, focuses on the development of a comprehensive longitudinal dataset by integrating clinical and demographic data with multiple forms of environmental exposures. To capture both short- and long-term effects on MS progression, environmental features were aggregated across multiple temporal windows, ranging from one week to several months prior to each patient visit. As missing data pose a major challenge in medical research, an advanced imputation technique is proposed for longitudinal datasets that consistently outperforms a wide range of standard baseline methods, leading to more robust subsequent analyses.

Aim 2, addressed in Chapter 4, investigates the relationship between environmental exposures and disease progression. For this purpose, Continuous Time Markov Model (CTMM) were applied to model transitions between disability states, taking advantage of their ability to handle irregular follow-up intervals and to capture both progression and potential improvement. The most notable finding is that several environmental exposures, including Nitrogen Dioxide (NO_2), Ozone (O_3), and global radiation, exert a stronger-than-expected influence on transitions between disability states when disease progression is considered alongside other exposures with accepted but less pronounced effects.

Aim 3, addressed in Chapter 5, focuses on developing a unified framework to forecast MS Severity Score (MSSS) classes through sequential data modeling using one of the integrated datasets developed in this research. This study pursues two main objectives. The first, and most central, is to forecast MSSS class, a more recent and refined measure of MS progression compared with Expanded Disability Status Scale (EDSS). The second is to assess the contribution of environmental exposures to this predictive task, specifically to determine their relative importance compared with clinical and demographic variables. This analysis is particularly relevant for forecasting the severity class at a patient's next clinical visit, an outcome of direct practical value for

clinicians. Models incorporating environmental data performed comparably to, or better than, those using only clinical variables. The Recurrent Neural Network (RNN) model achieved the best performance, with an average Area Under the Curve of 0.838 when environmental data were included and four prior visits were used as input. Moreover, SHAP-based feature importance analyses ranked environmental variables such as PM_{10} , $\text{PM}_{2.5}$, NO_2 , precipitation, and humidity among the top predictors.

Abstract (Italian)

La MS è diventata un tema di ricerca sempre più centrale negli ultimi anni, spinta dalla sua crescente prevalenza e dal suo rilevante impatto sulla salute pubblica. Si tratta di una patologia neuroinfiammatoria cronica e permanente che compromette progressivamente la funzione neurologica e conduce spesso a una disabilità significativa. Nonostante i progressi terapeutici che rallentano l'attività di malattia, la MS rimane una condizione cronica, e l'identificazione dei fattori che guidano la progressione della malattia è fondamentale per una gestione a lungo termine e per il miglioramento della qualità della vita. Sebbene i determinanti clinici e demografici della progressione siano ben consolidati, il ruolo delle esposizioni ambientali risulta ancora meno chiaramente compreso.

Questo lavoro è svolto nell'ambito del progetto *BRAINTEASER*, che mira a supportare l'assistenza ai pazienti con MS e ALS basata su AI, integrando dati clinici e ambientali provenienti da tre Paesi europei (Spagna, Italia e Portogallo). In questo contesto, il lavoro indaga il ruolo delle esposizioni ambientali, in particolare l'inquinamento atmosferico e le condizioni meteorologiche, nella progressione e nella predizione della MS, in combinazione con informazioni cliniche e de-

mografiche.

Lo studio è organizzato attorno a tre obiettivi principali. **Obiettivo 1**, affrontato nel Capitolo 3, si concentra sullo sviluppo di un dataset longitudinale completo mediante l'integrazione di dati clinici e demografici con diverse tipologie di esposizioni ambientali. Per catturare sia gli effetti a breve sia quelli a lungo termine sulla progressione della MS, le variabili ambientali sono state aggregate su più finestre temporali, che vanno da una settimana a diversi mesi precedenti ciascuna visita del paziente. Poiché i dati mancanti rappresentano una sfida rilevante nella ricerca medica, viene proposta una tecnica avanzata di imputazione per dataset longitudinali che supera costantemente un'ampia gamma di metodi baseline standard, conducendo ad analisi successive più robuste.

Obiettivo 2, affrontato nel Capitolo 4, analizza la relazione tra le esposizioni ambientali e la progressione della malattia. A tal fine, sono stati applicati i CTMM per modellare le transizioni tra stati di disabilità, sfruttando la loro capacità di gestire intervalli di follow-up irregolari e di catturare sia la progressione sia il potenziale miglioramento. Il risultato più rilevante è che diverse esposizioni ambientali, tra cui NO_2 , O_3 e la radiazione globale, esercitano un'influenza maggiore del previsto sulle transizioni tra stati di disabilità quando la progressione della malattia viene considerata insieme ad altre esposizioni con effetti accettati ma meno pronunciati.

Obiettivo 3, affrontato nel Capitolo 5, si concentra sullo sviluppo di un framework unificato per la previsione delle classi di MSSS attraverso la modellazione sequenziale dei dati utilizzando uno dei dataset integrati sviluppati in questa ricerca. Questo studio persegue due obiettivi principali. Il primo, e più centrale, è la previsione della classe MSSS, una misura più recente e raffinata della progressione della MS rispetto all'EDSS. Il secondo è la valutazione del contributo delle esposizioni ambientali a questo compito predittivo, in particolare per determinarne l'importanza relativa rispetto alle variabili cliniche e de-

mografiche. Questa analisi è particolarmente rilevante per la previsione della classe di gravità alla successiva visita clinica di un paziente, un esito di diretto valore pratico per i clinici. I modelli che incorporano dati ambientali hanno mostrato prestazioni comparabili o superiori rispetto a quelli che utilizzano esclusivamente variabili cliniche. Il modello RNN ha ottenuto le migliori prestazioni, con un'Area Under the Curve media pari a 0.838 quando i dati ambientali sono stati inclusi e sono state utilizzate come input quattro visite precedenti. Inoltre, le analisi di importanza delle caratteristiche basate su SHAP hanno collocato variabili ambientali quali PM_{10} , $PM_{2.5}$, NO_2 , precipitazioni e umidità tra i principali predittori.

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Chapter 1

Introduction

MS is a complex and unpredictable disorder of the Central Nervous System (CNS) that interferes with the transmission of signals within the brain and between the brain and the rest of the body. It occurs when the immune system mistakenly attacks the myelin sheath, the protective layer surrounding nerve fibers. This damage disrupts communication between the brain and the rest of the body, leading to a wide range of neurological symptoms. Over time, these disruptions can result in progressive physical and cognitive disabilities. Globally, nearly three million people are affected by MS, with particularly high prevalence in Europe and Italy [1].

Understanding the evolution of disease processes and the impact of interventions over time requires longitudinal data. Such data are collected in a variety of settings, ranging from randomized trials to retrospective cohort studies. In some datasets, both the number and the timing of observations differ from one patient to another, and often no two patients share the same observation time.

Emerging evidence [2, 3, 4, 5] suggests that environmental exposures—particularly air pollution and weather conditions—may signif-

icantly influence MS onset and progression. Recent studies [6, 7, 8, 9] have highlighted associations between pollutants such as PM₁₀, PM_{2.5}, NO₂, and Carbon Monoxide (CO) and increased MS disease activity or relapse rates. Understanding the influence of these exposures is particularly relevant given growing concerns about urban air quality and climate variability.

Although research on MS has advanced in recent years, there remains a major lack of real-world longitudinal datasets that integrate clinical, environmental, treatment, and demographic information. Without such datasets, it is difficult to fully model and understand the complex factors driving MS progression, which in turn limits the development of personalized prediction and treatment strategies. The *BRAINTEASER* project, a Horizon 2020 initiative funded by the European Union and launched in January 2021, aims to address this gap by combining health, environmental, and societal data to create advanced models for patient classification and disease monitoring in both ALS and MS. A key objective of the project is the construction of a comprehensive dataset that brings together clinical, demographic, environmental, and treatment features.

As part of this project, we pursue several objectives: *first*, to integrate and preprocess a comprehensive longitudinal dataset by addressing missing values and ensuring data completeness; *second*, to analyze the relationship between environmental exposures and MS progression; and *third*, to forecast future disease trajectories using the integrated dataset. Ultimately, the goal is to support the development of more personalized and context-aware clinical decision support systems for MS management.

1.1 Background

1.1.1 Multiple Sclerosis

When the protective myelin sheath around nerve fibers is damaged, communication between the brain and the rest of the body becomes disrupted. This is what occurs in MS, which was first described in 1868 by Jean-Marie Charcot [10]. It is the most common long-term inflammatory disease of the CNS, in which the immune system mistakenly attacks the myelin (see Figure 1.1) [11, 12]. This damage can lead to a wide range of neurological symptoms that vary greatly from person to person. These may include vision problems, muscle weakness, fatigue, balance issues, bladder dysfunction, memory and cognitive difficulties, and mood disorders [11]. Although the precise etiology of MS is not fully understood, it is generally believed to result from a complex interplay of genetic susceptibility, environmental exposures, and immune system dysregulation. A family history of the disease is also associated with an increased individual risk [13].

According to the latest data from the Atlas of MS [14], approximately three million people worldwide are currently living with the disease, including about one million in Europe and around 133,000 in Italy, which has one of the highest prevalence rates. The global number of MS cases has risen from 2.3 million in 2013 to 2.8 million in 2023, indicating a growing worldwide burden of MS.

On average, one person is diagnosed with MS every five minutes, and the disease is more prevalent at higher latitudes [12]. MS usually begins between the ages of 20 and 40, although it can sometimes appear in children (less than 1% of cases) or later in life (2–10% of cases after age 50) [15, 16]. The condition can be mild for some individuals, but for others it may lead to serious physical and mental challenges over time. Women are affected two to three times more often than men [13, 17].

1.1. Background

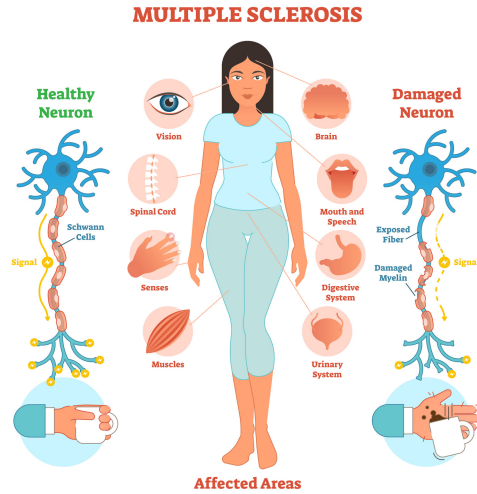


Figure 1.1: Healthy neuron vs damaged neuron in MS patients

1.1.2 Environmental Exposure

The environment in which individuals live plays a crucial role in shaping overall health, influencing both the onset and progression of many chronic diseases, including neurodegenerative and autoimmune disorders. In the case of MS, several environmental exposures—particularly air pollution—have been investigated for their potential role in increasing disease risk and worsening clinical outcomes. Air Pollution (AP), which includes harmful substances such as Particulate Matter (PM) (PM_{2.5} and PM₁₀), NO₂, O₃, CO, and Sulfur Dioxide (SO₂), may disrupt immune regulation and compromise biological barriers, thereby contributing to inflammation and CNS damage [18]. Some studies have reported significant associations between exposure to PM and increased risks of MS relapse or hospitalization [7, 3, 19], while others suggest that pollutants such as NO₂ and O₃ are linked to seasonal

1.1. Background

variations in relapse patterns [20, 21]. However, findings are not fully consistent, as several large cohort studies have reported no clear association between air pollution and MS incidence or disease activity [18, 22, 23, 24].

1.1.3 BRAINTEASER Project

This research was conducted within the Bringing AI home for a better care of Amyotrophic Lateral Sclerosis and Multiple Sclerosis (BRAINTEASER) project, which aimed to improve the quality of life of ALS and MS patients by leveraging AI to model disease progression and support personalized and timely clinical care.

A major outcome of the project was the release of four curated datasets containing clinical and environmental data from nearly 3,000 ALS and MS patients, collected from routine clinical practice and made publicly available as a curated resource [25]. These datasets provide a realistic representation of real-world data encountered by AI-based disease progression models and have undergone both manual and automated quality control. Their validity was further demonstrated through three editions of the Intelligent Disease Progression Prediction challenges organized within the Conference and Labs of the Evaluation Forum (CLEF) initiative [26, 27, 28].

The project integrated large-scale clinical data with patient-generated and environmental information collected via cost-effective sensors and European open-source environmental platforms. All solutions were developed following agile, user-centered design principles that addressed medical, technological, and social needs.

The BRAINTEASER consortium comprised 11 partners from six European countries, spanning academia, healthcare institutions, industry, and non-profit organizations. The team was multidisciplinary and gender-balanced. Some of the partners illustrated in Figure 1.2 were:

1.1. Background

- UPM; Universidad Politécnica de Madrid (Spain) — *Project coordinator*
- UniPd; Università degli Studi di Padova (Italy)
- FC.ID; FCIÊNCIAS.ID Associação para a Investigação e Desenvolvimento de Ciências (Portugal)
- UniTo; Università degli Studi di Torino (Italy)
- GIMM; Instituto de Medicina Molecular – João Lobo Antunes (Portugal)
- Sermas; Servicio Madrileño de Salud (Spain)
- Fondazione Istituto Neurologico Nazionale Casimiro Mondino (Italy)



Figure 1.2: Brainteaser partners

Environmental data integration, including air pollution and weather information, was carried out by the University of Pavia in collaboration with the Fondazione Istituto Neurologico Nazionale Casimiro Mondino. Overall, the project served as a proof of concept for the application of AI in real-world clinical settings and contributed to the transition from reactive to predictive models of healthcare.

1.2 Motivation and Research Questions

The main motivation behind this research is to understand how environmental exposures affect the progression of MS. While numerous studies [29, 30, 31, 32, 33, 34] have employed statistical and Machine Learning (ML) approaches to predict MS progression, most have focused solely on clinical and demographic data. Far less attention has been given to integrating longitudinal clinical records with environmental data collected from the nearest monitoring stations for each patient. Such integration is essential for accurately assessing how real-world environmental variability may influence disease dynamics.

To address this gap, we present novel AI-based frameworks that combine clinical, demographic, and environmental data to both predict MS progression and analyze the impact of environmental exposures. By applying a diverse range of analytical models, including statistical methods, ML, and Deep Learning (DL), we aim to provide both accurate predictions and deeper insights into how external environmental conditions relate to changes in disability states over time.

More specifically, this research addresses the following key questions:

R_1 : How can an integrated longitudinal dataset be constructed by combining multiple longitudinal data sources, including clinical, environmental, treatment, and demographic data, to support comprehensive MS progression analysis?

R_2 : How should clinical and environmental data be preprocessed to effectively handle missingness in longitudinal MS studies?

R_3 : To what extent do environmental factors contribute to MS progression, and does their impact differ across various stages of disability?

R_4 : Can probabilistic models such as CTMM effectively capture disability transitions?

R_5 : How well do sequential data modeling approaches predict MS pro-

1.3. Contribution of the Thesis

gression when incorporating environmental inputs?

R_6 : What are the short- and long-term effects of specific pollutants on MS stages?

R_7 : Can environmental exposures surpass well-established clinical and demographic factors in influencing MS progression?

The solutions proposed in this thesis are designed to complement and coexist with existing approaches for predicting MS progression. Rather than replacing current models, this work extends them by integrating environmental exposure as an additional layer of context in disease modeling. In the next section, we present the key contributions of this thesis and provide a detailed explanation of each.

1.3 Contribution of the Thesis

This thesis addresses the complexity of MS progression by adopting a comprehensive, multi-perspective approach that integrates environmental, clinical, treatment, and demographic factors. The resulting dataset is then employed in advanced statistical, ML, and DL methods to analyze disease progression and to investigate the relationship between environmental exposures and disease dynamics (see Figure 1.4).

Accordingly, the work is structured around three specific aims, illustrated in Figure 1.3:

First, we construct an integrated longitudinal dataset that unifies heterogeneous data sources, including clinical records, environmental exposures, treatment data, and demographic information. The integration strategy is designed to capture both short-term (weeks preceding clinical visits) and long-term (inter-visit intervals) dynamics, thereby enabling temporally granular analyses. We then propose a tailored preprocessing framework for handling missing values in longitudinal datasets. The methodology includes advanced imputation

1.3. Contribution of the Thesis

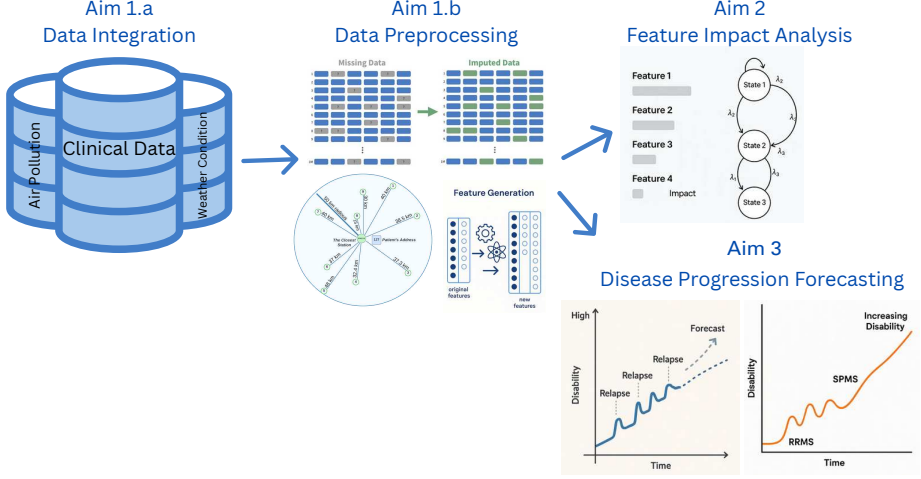


Figure 1.3: Specific aims of the research

strategies suitable for time-series data, ensuring a reliable representation of both clinical and environmental variables over time. This work directly addresses R_1 and R_2 .

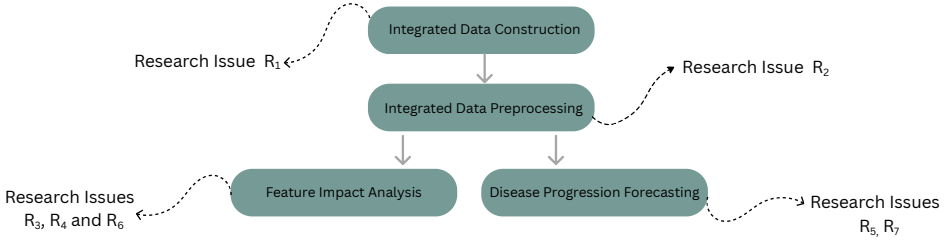


Figure 1.4: Thesis contribution with corresponding research issue

Second, we investigate the influence of environmental exposures on MS progression using a CTMM. This approach accommodates irregular visit intervals and enables probabilistic modeling of transitions

between disability states, thereby addressing R_3 , R_4 , and R_6 .

Third, we introduce an AI platform for forecasting the MSSS class at the next visit of MS patients using sequential data modeling. This component also highlights the potential contribution of environmental features to predictive tasks, thereby addressing R_5 and R_7 .

In each chapter, we identify the research problem and explain how it is investigated using appropriate methods, justify the chosen approach, and demonstrate how it contributes to addressing the overall research questions of the thesis.

1.4 Outline of the Thesis

The remainder of this thesis is structured as follows. Chapter 2 provides essential background information on MS. It outlines the major clinical courses of the disease and the methods used to assess its progression. The chapter also synthesizes existing literature on MS progression and environmental exposures, with a particular focus on air pollution.

Chapter 3 introduces the primary datasets employed in this research. It details the collection of air pollution and meteorological data, their linkage to patient records, and the preprocessing steps undertaken to construct an integrated and comprehensive dataset. Special attention is given to the strategies used to address missing data across both data sources. Furthermore, the chapter reviews state-of-the-art imputation techniques for longitudinal data and provides justification for the selected approach.

Chapter 4 focuses on the statistical modeling of the relationship between environmental exposures and MS progression using the integrated dataset. The methodology is described in detail, with particular attention given to its suitability for the research context.

Chapter 5 addresses the prediction of MS progression through se-

1.4. Outline of the Thesis

quential data modeling. It details the use of temporal data to predict the MSSS and examines the potential role of environmental factors in shaping predictive performance.

Finally, Chapter 6 concludes the thesis by providing concise answers to the research questions, summarizing the principal findings, and outlining potential directions for future work.

Chapter 2

Literature Review

This chapter provides a comprehensive overview of MS progression from clinical, environmental, and AI perspectives. It begins by defining the clinical aspects of MS progression, followed by an exploration of environmental influences, with particular attention given to the exposome and external factors such as air pollution and weather conditions. The chapter then reviews recent research employing AI techniques—ranging from statistical modeling to machine and deep learning—for predicting disease progression. Finally, it addresses the challenge of missing data in longitudinal clinical records and summarizes the imputation strategies proposed in this research.

2.1 Clinical Progression of MS

2.1.1 MS Phenotypes

In 1996, the International Advisory Committee on Clinical Trials in Multiple Sclerosis (IACCTMS), now supported by the European Com-

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mittee for Treatment and Research in MS and the U.S. National MS Society, published a seminal paper that established the clinical course classifications of MS [35]. These classifications were revised in 2013 to incorporate advances in the understanding of disease mechanisms and progression [36]. The update introduced additional descriptors to more accurately reflect a patient’s current disease status and to capture variability in progression patterns.

The classification of MS is important because, *first*, it facilitates effective communication between clinicians and patients; *second*, it provides a standardized framework for studying the natural history of the disease and identifying prognostic markers; and *third*, it helps reduce heterogeneity in clinical trial populations, thereby improving the reliability and generalizability of study findings [17].

Each subtype reflects a distinct pattern of disease activity and progression and therefore plays a critical role in guiding therapeutic decisions [37, 11]. The four main recognized forms of MS include: (1) *Relapsing Remitting MS (RRMS)*, (2) *Secondary Progressive MS (SPMS)*, (3) *Primary Progressive MS (PPMS)*, and (4) *Progressive Relapsing MS (PRMS)*.

MS phenotype diagnosis is typically guided by the McDonald criteria, a widely accepted set of guidelines that combine clinical evaluation with supporting evidence from Magnetic Resonance Imaging (MRI), evoked potentials, and immunologic findings in Cerebrospinal Fluid (CSF) [38]. Originally introduced in 2001 by an international panel led by neurologist W. Ian McDonald [39], these criteria have been revised multiple times—in 2005, 2010, and 2017—to enhance diagnostic precision and allow for earlier confirmation of the disease. The updated versions reflect advances in imaging techniques and a deeper understanding of MS pathology, making the McDonald criteria a cornerstone in both clinical and research settings [38].

RRMS, the most common form of MS, represents the initial phase of the disease and affects approximately 85% of patients. It is defined

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by episodes of neurological symptom worsening (relapses) followed by periods of partial or complete recovery (remission) [40]. Current smoking has been associated with a 43.9% increased risk of relapse, while having three or more comorbidities (coexisting health conditions) also elevates relapse risk. In contrast, older age has been linked to a reduced risk of relapse [41]. Although patients with RRMS may appear stable during remission, they can still experience difficulties with certain cognitive functions, particularly those involving reasoning, planning, and self-control [42].

Additionally, recovery from relapses usually occurs within one year and appears to depend primarily on relapse severity rather than on demographic factors such as age or sex [43].

SPMS, the second most common form of MS, develops after an initial RRMS phase. This transition occurs in more than one-third of patients within 8 years, in approximately half within 15 years, and in up to two-thirds within 30 years. It is characterized by a gradual and often irreversible decline in neurological function, with or without relapses, leading to progressive physical and cognitive impairment. Despite its prevalence, diagnosis is frequently delayed—sometimes by as much as three years—due to both clinical- and patient-related factors [44].

The early stages of SPMS are often difficult to recognize because the brain can temporarily compensate for nerve cell loss. This period may represent the optimal window for initiating treatment. The brain adapts by recruiting neurons from other regions, activating homologous areas in the opposite hemisphere, and reorganizing connections near lesions [45, 46]. Recent studies indicate that new therapies and first-generation Disease Modifying Therapies (DMT)s can reduce or delay the risk of progression to SPMS, with treated patients progressing significantly less often than those in older, untreated cohorts [47, 48].

PPMS is defined by a steady worsening of symptoms from disease

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onset, without clear relapses or remission. It typically begins about 10 years later than RRMS (with an average age of onset of approximately 40 years compared to 30 years) and at a similar age to SPMS. Diagnosis can be challenging because many patients do not exhibit typical features, such as symptoms occurring in different anatomical locations or at different points in time [49]. PPMS accounts for approximately 10–15% of all MS cases. Unlike relapsing forms of the disease, which are more common in women, PPMS affects men and women equally [50].

In this form of MS, inflammation often occurs behind an intact blood–brain barrier, which may contribute to reduced treatment effectiveness. However, studies indicate that early initiation of treatment with ocrelizumab can slow disease progression and lead to improved long-term outcomes [51]. Disease progression in PPMS is thought to result from a combination of immune-mediated damage and impaired cellular energy metabolism. Patients who have experienced relapses prior to diagnosis often exhibit patterns of disability progression similar to those observed in relapsing forms of MS. This observation supports the hypothesis that PPMS may begin as a subclinical process before symptoms become clinically apparent [50].

PRMS is the least common form of MS, affecting approximately 5% of patients. Similar to PPMS, it involves a steady worsening of neurological function from disease onset, but it is distinguished by the presence of superimposed relapses. Individuals with this phenotype experience continuous disability progression along with occasional episodes of new or worsening symptoms. Because PRMS begins with gradual worsening, it is often initially misdiagnosed as PPMS until relapses become apparent. Recent research has shown that relapses in PRMS may be more frequent than previously expected [52].

Symptoms of PRMS may include vision problems, dizziness, mood changes, and bladder or sexual dysfunction [37, 11]. Owing to the rarity of this form, information regarding its specific clinical features

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and long-term progression remains limited.

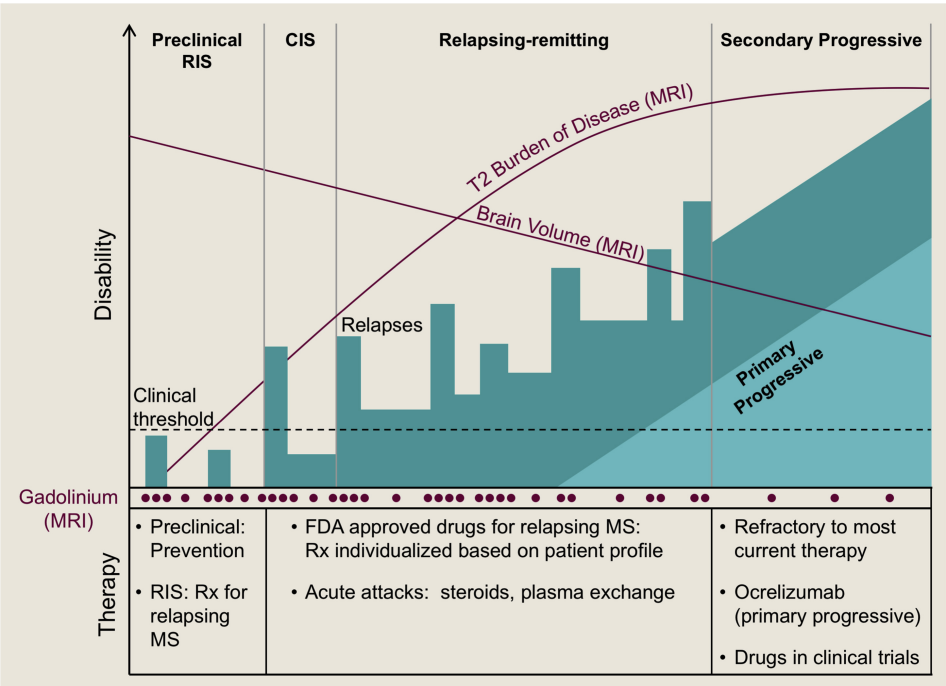


Figure 2.1: Timeline of multiple sclerosis progression: from preclinical stage to progressive disease [53]

There are also two early or preclinical forms of MS: *Clinically Isolated Syndrome (CIS)* and *Radiologically Isolated Syndrome (RIS)*.

CIS refers to a first, isolated episode of neurological symptoms suggestive of MS, but not sufficient to meet the full diagnostic criteria. Approximately 60–70% of individuals with CIS develop MS within 20 years [54], and around 30% experience a second clinical attack leading to a definitive diagnosis within the first year [55]. When assessing a patient with CIS, clinicians must determine whether the episode can be explained by an alternative condition. They must also decide

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whether treatment should be initiated to promote recovery or to delay conversion to clinically definite MS. The risk of conversion can be estimated using predictive factors, and accurate distinction between CIS and other transient neurological syndromes is essential, as early recurrence is associated with poorer long-term outcomes [56].

In contrast, RIS was formally defined in 2009 and refers to individuals in whom MRI scans performed for unrelated reasons (e.g., headaches or trauma) reveal brain lesions typical of MS in the absence of clinical symptoms.

Approximately half of individuals with RIS convert to MS within 10 years, most commonly developing RRMS. Some cases, however, may progress directly to PPMS. Currently, there is no approved treatment for RIS [57]. Moreover, this silent preclinical phase has also been observed in pediatric populations, indicating that RIS can occur across all age groups [58]. As illustrated by Baecher-Allan et al. [53], Figure 2.1 depicts the various stages of MS, suggesting that the disease likely begins prior to clinical manifestation at the stage of RIS, which can be detected by MRI.

The subsequent stage is CIS, after which most individuals enter the relapsing–remitting phase, characterized by periods in which symptoms appear and resolve. Over time, the disease often transitions into a progressive stage, during which symptoms steadily worsen. MRI findings in MS frequently demonstrate disruption of the blood–brain barrier and infiltration of immune cells into the brain. Additional imaging features include an increased burden of T2 lesions and progressive brain atrophy. While many treatments are effective in managing the relapsing phase of MS, therapeutic options for the progressive stage remain limited.

2.1.2 Disability Progression Measurements

MS progression refers to the gradual worsening of the disease after the onset of initial symptoms and can occur across all disease subtypes, even in the absence of relapses [59]. While unofficial terms such as *benign* ($\text{EDSS} \leq 3$ after ≥ 15 years) and *malignant* ($\text{EDSS} \geq 6$ within 5 years) are sometimes used to describe the pace and severity of progression, they are not formally recognized disease phenotypes [60]. Disease progression reflects the long-term accumulation of disability, whether it develops slowly with minimal impact or advances rapidly, with frequent and severe relapses leading to substantial functional decline.

The progression of MS is driven by three key biological processes. These processes often occur concurrently, and their relative contribution and temporal order may vary across individuals:

- **Neurodegeneration:** Neurons in the brain and spinal cord progressively sustain damage and undergo cell death, impairing the transmission of neural signals.
- **Inflammation:** Aberrant immune responses target components of the CNS, leading to inflammation, tissue damage, and demyelination, which underlies the autoimmune nature of MS.
- **Breakdown of CNS Repair and Tolerance:** As the disease advances, the capacity of the brain and spinal cord to repair damage or compensate for functional loss diminishes, resulting in sustained neurological decline.

In general, five years after symptom onset, more than half of individuals exhibit only mild impairment, approximately 40% develop moderate disability, and fewer than 10% experience severe, potentially life-threatening complications [30].

“How am I doing, Doctor?” This fundamental question underscores the importance of quantifying disability in MS. To address it, two primary measures are commonly used, as outlined below.

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The EDSS, developed by neurologist John Kurtzke [61], is the most widely used tool for assessing and tracking disability in MS. It enables neurologists to monitor changes in a patient's condition over time. The scoring process involves two main steps.

First, the clinician evaluates eight key Functional System (FS) scores. These scores correspond to specific FSs within the nervous system, each governing distinct aspects of neurological function. Table 2.1 summarizes the meaning of each FS score and its clinical relevance to MS progression. Each FS is graded on an ordinal scale ranging from 0 (no disability) to 5 or 6, reflecting increasing levels of neurological impairment.

2.1. Clinical Progression of MS

Table 2.1: Meaning of FSs and their clinical relevance to MS progression

Functional Score	Description	Meaning and Relevance to MS Progression
Pyramidal	Motor strength and voluntary movement	Increasing scores indicate progressive weakness, ranging from mild paresis to severe paraparesis, hemiplegia, or quadriplegia.
Cerebellar	Coordination, balance, tremor	Higher scores reflect worsening ataxia and impaired limb or trunk coordination, leading to gait instability and increased fall risk.
Brainstem	Cranial nerve function (speech, swallowing, eye movement)	Scores correspond to increasing disability, including severe nystagmus, dysarthria, dysphagia, or impaired extraocular movements.
Sensory	Touch, pain, proprioception, vibration	Higher values indicate mild-to-severe sensory loss, contributing to imbalance and reduced awareness of limb position.
Visual	Visual acuity and visual field integrity	Scores progress from small scotomas to major visual field restrictions or near-blindness.
Bladder&Bowel	Autonomic control of urinary and bowel function	Increasing impairment ranges from urgency to incontinence, catheter dependence, or complete bladder and bowel dysfunction.
Mental	Cognition, mood, and mental status	Higher scores indicate increasing cognitive decline, from mild impairment to severe dysfunction or dementia.
Other	Walking ability and reliance on support	Scores reflect reduced walking distance and increasing dependence on support, progressing ultimately to wheelchair use.

Once these functional areas are evaluated, the results are combined

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with the patient’s walking ability to assign an overall EDSS score. The scale ranges from 0, indicating a normal neurological examination, to 10, representing death due to MS [62, 28]. Notably, the first score above 0 is 1.0, not 0.5. From that point onward, the scale increases in increments of 0.5 to capture progressive levels of clinical deterioration. Figure 2.2 illustrates the full scale, along with the relationship between scores, disability stages, and disease progression.

Scores from 1.0 to 4.5 generally indicate preserved ambulation without major limitations, whereas scores from 5.0 to 9.5 reflect increasing walking impairment or the need for assistance. Some experts consider scores between 1.0 and 4.0 to represent a milder (or “benign”) disease course; however, others argue that this classification depends on additional factors, such as disease duration and the rate of symptom progression [63].

Although not all functional systems are equally affected in every patient, studies indicate that the pyramidal, cerebellar, and sensory systems are most commonly involved in MS progression [64, 65].

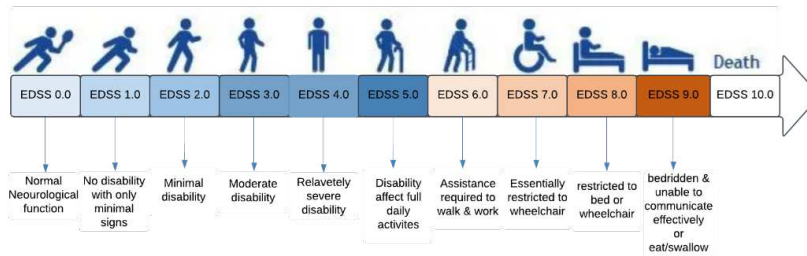


Figure 2.2: EDSS; stages of MS progression and functional impact

One of the main objectives of this research is to identify the most significant clinical and environmental factors contributing to MS progression, as explored in Chapters 4 and 5.

That said, the use of the EDSS to assess MS progression has notable

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limitations. Its nonlinear structure constrains its ability to distinguish between rapid disability accumulation and slower, long-term progression, particularly in the early stages of the disease. In addition, the EDSS does not account for disease duration, which is an important determinant of disability accumulation over time.

The MSSS was therefore developed as a modification of the EDSS [66, 67, 68]. The MSSS provides a time-adjusted measure of disease severity by ranking each patient's EDSS score relative to those of patients with comparable disease duration, thereby reducing bias associated with disease length. This approach yields a more robust assessment of relative disease progression than unadjusted measures such as the EDSS alone.

Methodologically, patients are grouped into deciles based on disease duration, and EDSS scores within each group are ranked to determine relative disability severity. Higher ranks indicate faster-than-average disability accumulation for a given disease duration, whereas lower ranks reflect slower progression. This simple principle underlies the concept of a rank-based severity score. Although the MSSS has been shown to identify individuals at risk of rapid disease progression [69], it has rarely been adopted as a predictive endpoint in AI-based modeling studies.

Researchers have found the MSSS to be one of the most effective methods for identifying differences in progression rates among patients with MS. In other words, it enables more accurate classification of patients based on the speed at which their condition progresses [68, 69].

Accordingly, patients with lower MSSS values tend to experience slower disease progression, whereas those with higher scores are more likely to deteriorate at a faster rate. The model operates under the assumption that a patient's decile ranking within the scale remains a stable and reliable indicator of their disease trajectory over time [70, 71, 72].

Figure 2.3 presents the global MSSS, derived from data on 9,892

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European patients with MS, which serves as a reference population in related studies. A patient's MSSS is determined by identifying the cell corresponding to their EDSS score (column) and the number of years since disease onset (row). The deciles are color-coded, providing a visual representation of how progression rates vary across different disease durations [68].

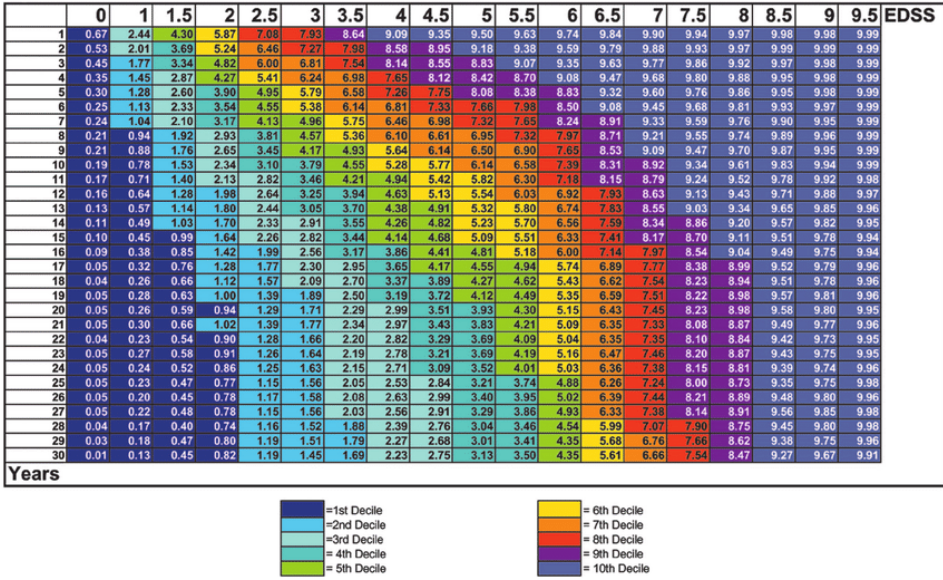


Figure 2.3: Global MSSS generated from 9,892 European patients. The MSSS for an individual patient is ascertained by finding the column corresponding to the patient's EDSS and the row corresponding to the number of years since the MS onset. Deciles are color coded to show the pattern of disease progression at different disease durations [68]

While the subsequent analyses make use of both the EDSS and the MSSS, this thesis introduces a novel metric, termed *"Progression"*, to quantify disability progression. This metric integrates the two clinical measures while explicitly accounting for the time interval between

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patient visits. Given the longitudinal nature of the dataset—which contains variable numbers of observations and irregular follow-up intervals across patients—the Progression formula was designed to yield a normalized and interpretable outcome measure suitable for applications in AI.

The metric classifies MS progression into four clinically meaningful categories: *Improvement*, *Stable*, *Normal Progression*, and *Significant Progression*. Classification is achieved by quantifying changes in the MSSS over time and relating those changes to the level of disability indicated by the EDSS. This approach may be feasible when a sufficient number of patients exhibiting progression are available; however, this was not the case in the dataset used for the present research.

The formulation begins by computing the rate of change in the MSSS score between two consecutive clinical visits:

$$z = \frac{\delta \text{MSSS}}{\delta T} = \frac{\text{MSSS}_t - \text{MSSS}_{t-1}}{\text{visit}_t - \text{visit}_{t-1}} \quad (2.1)$$

where: MSSS_{t-1} is the MSSS score of previous visit and visit_{t-1} is the previous visit date. This means that:

- If $z > 0$, MSSS is increasing $\Rightarrow$ disease progression.
- If $z < 0$, MSSS is decreasing $\Rightarrow$ disease improvement.
- If $z = 0$, MSSS is unchanged $\Rightarrow$ stable condition.

To enhance the clinical interpretability of this rate, a binary function is incorporated to assess whether the EDSS score at time t exceeds a clinically relevant threshold. Although the exact threshold may vary depending on clinical judgment, an EDSS score of 3 or higher is commonly associated with moderate-to-severe physical disability:

$$f(\text{EDSS}_{t+1}) = \begin{cases} 0 & \text{if } \text{EDSS}_t < 3 \\ 1 & \text{if } \text{EDSS}_t \geq 3 \end{cases} \quad (2.2)$$

This means that:

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- If EDSS is below 3, the corresponding change in MSSS is considered less clinically impactful.
- If EDSS is 3 or more, the change is treated as more clinically significant.

Next, the sign function is applied to determine whether the change in MSSS is positive, negative, or neutral, thereby transforming the rate z into a categorical indicator:

$$\text{sgn}(z) = \begin{cases} 1 & \text{if } z > 0 \\ 0 & \text{if } z = 0 \\ -1 & \text{if } z < 0 \end{cases} \quad (2.3)$$

The rate of change in MSSS (z) is then combined with the EDSS-based severity flag to construct an adjusted progression measure y_t :

$$y_t = z + [\text{sgn}(z \cdot f(\text{EDSS}_t))] \quad (2.4)$$

This formula adjusts the raw MSSS change (z) by +1, 0, or -1 only if the EDSS score is within the clinically significant range ($\text{EDSS}_t \geq 3$). It helps differentiate minor or borderline changes from those that are clinically meaningful. Finally, the computed value y_t is used to classify disease progression into one of four categories:

$$o_{t+1} = \begin{cases} \text{Stable} & \text{if } y_t = 0 \\ \text{Improvement} & \text{if } y_t \in (-\infty, 0) \\ \text{Normal Progression} & \text{if } y_t = z \\ \text{Significant Progression} & \text{if } y_t \neq z \end{cases} \quad (2.5)$$

where

- **Stable:** No MSSS change and no EDSS severity trigger.
- **Improvement:** MSSS has decreased.
- **Normal Progression:** MSSS increased, but EDSS did not indicate severe disability.

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- **Significant Progression:** MSSS increased and EDSS confirmed meaningful progression.

2.1.3 MS Risk Factors and Biomarkers

This section reviews key risk factors that may influence the progression of MS, together with recently investigated biomarkers. While numerous studies have examined these factors, the discussion focuses on a subset of the most salient findings, including genetic predisposition [73], vitamin D deficiency [74], smoking [75], and female sex [76].

Studies indicate that individuals with a family history of MS have a higher risk of developing the disease, suggesting that *genetic factors* play an important role [77]. First-degree relatives of patients with MS have a 2–4% lifetime risk of developing the condition, compared with approximately 0.1% in the general population [78]. More than 200 genetic variants have been linked to MS susceptibility, with the strongest associations located in the Major Histocompatibility Complex (MHC) region, particularly the HLA class II histocompatibility antigen, DRB1 beta chain (HLA-DRB1) gene [79, 80, 77].

Overall, genetic factors are estimated to account for approximately 30% of MS risk [81]. Among monozygotic twins, if one individual is affected by MS, the risk for the co-twin is approximately 25%, whereas this risk decreases to around 5% in dizygotic twins [82].

Vitamin D plays an important role in modulating MS progression. Low serum levels have been linked to an increased risk of developing MS [83] and have also been associated with more frequent relapses, greater disability, and increased lesion burden on MRI, underscoring its potential relevance in disease management [83, 84, 85, 86].

In contrast, Langlois et al. [87] reported that vitamin D supplementation does not consistently reduce relapse rates or disability progression, although it may decrease the number of new MRI lesions.

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Similarly, Cassard et al. [88] found no significant reduction in relapse risk with high-dose supplementation in treated patients with RRMS. Overall, current clinical evidence remains insufficient to support vitamin D supplementation as a therapeutic intervention for MS. Nevertheless, it continues to be an area of active investigation, particularly in early or pre-diagnostic stages of the disease, warranting further research.

MS is more prevalent in *women*, who are diagnosed two to three times more frequently than men—a disparity that has increased steadily in recent decades [89]. Although the underlying causes of this sex difference remain unclear, proposed contributing factors include hormonal influences, lifestyle and dietary patterns, reproductive history, and occupational roles [90, 91]. Sex also influences the clinical course of MS: women tend to experience more frequent relapses, particularly before menopause, whereas men more commonly develop progressive disability with fewer inflammatory episodes. Recognizing these sex-specific differences is essential for refining diagnosis, personalizing treatment strategies, and improving clinical outcomes [92, 93].

Women are also more likely to be diagnosed with RRMS, and being of childbearing age may confer neuroprotective effects, potentially delaying cognitive decline and the onset of progressive MS, which is primarily associated with more severe long-term disability. Furthermore, emerging evidence suggests that parity may exert a protective influence. For example, studies indicate that having more children is associated with a reduced risk of a first demyelinating event, implying a possible immunomodulatory or suppressive effect. Pregnancy itself—particularly during the third trimester—has been linked to decreased relapse rates and reduced neurological symptom burden in women with MS [76].

Recent research has increasingly focused on identifying biological markers that provide measurable indicators of MS progression. Belien et al. [94] examined myeloid markers such as Chitinase-1 (CHIT1) and

2.2. Environmental Impact on MS Progression

Glycoprotein Non-Metastatic Melanoma Protein B (GPNMB) in CSF using longitudinal patient data and identified CHIT1 as a strong early biomarker for predicting faster disability progression through mixed-effects and ML models. In addition, combining protein biomarkers from cerebrospinal fluid (vitamin D binding protein, Factor I, and C1 inhibitor) and serum (Factor B, Interleukin-4 (IL-4), and C1 inhibitor) has been shown to significantly improve the accuracy of predicting time to the next relapse in MS compared with single-biomarker approaches. Time to EDSS 6 was most accurately predicted using CSF biomarkers (C9 and Neurofilament-light (Nf-L)) and serum biomarkers (Chitinase-3-like protein 1 (CHI3L1), C-C Motif Chemokine Ligand 27 (CCL27), vitamin D binding protein, and C1 inhibitor) [95].

Moreover, elevated levels of the chemokine C-X-C motif chemokine ligand 13 (CXCL13) and younger age have been associated with increased short-term disease activity in patients with RRMS. These markers may also help identify individuals with CIS who are likely to convert to RRMS within one year [96].

Beyond molecular biomarkers, lower Tapping Speed (TS), measured passively via smartphone-based assessment over one month, has emerged as a promising digital biomarker for predicting Progression Independent of Relapse Activity (PIRA) within one year. Patients experiencing PIRA exhibit significantly lower median and mean TS values, with thresholds of ≤ 3 and ≤ 3.7 keystrokes per second, respectively, being strongly associated with increased risk [97].

2.2 Environmental Impact on MS Progression

Several risk factors contributing to the progression of MS, along with emerging biomarkers that support disease management and inform treatment strategies, have been examined in the literature. However, the role of environmental exposures in MS progression remains

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comparatively underexplored.

Good health depends on a safe environment, including clean air, safe water, effective sanitation, and protection from hazardous chemicals, radiation, and unsafe working conditions [1]. For individuals with MS, who are particularly vulnerable due to immune dysfunction, these environmental factors are especially relevant. This section reviews the literature on environmental exposures in relation to MS progression and is organized into two parts: the first addresses the role of air pollution and weather conditions, while the second examines other components of the environmental exposome that may influence disease progression.

2.2.1 Air Pollution and Weather Conditions on MS progression

Air pollution, the second leading risk factor for noncommunicable diseases, represents a major global health challenge and is responsible for an estimated 6.7 million premature deaths each year [98, 1]. Major sources include industrial emissions, vehicle exhaust, and forest fires, which release six principal pollutants—PM (PM_{2.5} and PM₁₀), CO, O₃, NO₂, and SO₂—as defined by the World Health Organization (WHO) [1]:

- **PM** refers to inhalable particles composed of substances such as sulphates, nitrates, ammonia, black carbon, mineral dust, or water. These particles are classified by aerodynamic diameter, most commonly as PM_{2.5} and PM₁₀.
- **CO** is a toxic, colorless, and odorless gas released through incomplete fuel combustion.
- **O₃** is a major component of photochemical smog, formed through reactions between sunlight and precursor gases.
- **NO₂** is emitted primarily from fuel combustion associated with

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transportation and industrial activities.

- **SO₂** is a pungent gas released from the combustion of fossil fuels and the smelting of sulfur-rich ores.

Research on AP has been more extensive than that on weather conditions. Accordingly, both factors are analyzed in this thesis, with greater emphasis placed on AP while still accounting for weather-related influences. Given the limited number of studies specifically examining weather and MS progression, the scope is broadened to include associations with disease prevalence, relapse activity, and diagnosis, thereby providing a more comprehensive perspective on environmental influences in MS.

A 20% increase in cognitive decline was observed among individuals exposed to high levels of urban AP over a 20-year period in the United States [99]. In contrast, no significant association has been identified between AP—particularly PM—and MS progression in the same population [23]. More specifically, exposure to PM₁₀ has been significantly associated with an increased risk of MS, whereas other pollutants have not shown such associations [7].

Short-term exposure to air pollution 1–3 days prior to relapse has also been shown to substantially increase the likelihood of relapse events [3]. Additionally, exposure during the cold season has been linked to increased relapse rates [20], with the most pronounced impact on MS-related hospitalizations observed within 0 to 7 days following exposure [19]. It has further been suggested that air pollution may contribute to MS development in females [100].

Cortese et al. [101] proposed a potential mechanistic pathway whereby inhaled particulate matter stimulates the production of self-reactive Th17 cells in the lungs, which subsequently migrate via the bloodstream to the brain, thereby exacerbating MS through CNS inflammation.

Regarding PM_{2.5}, significant associations have been reported with an increased risk of pediatric MS [2], and exposure has been shown to

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nearly double MS-related mortality among females in colder climates [6]. Elevated $\text{PM}_{2.5}$ levels have also been linked to lower cognitive memory scores in older women [102]. In Italy, several studies [103, 104, 19] have reported strong correlations between air pollution and MS, including increased disease prevalence in the Province of Padua [104].

Although multiple studies have investigated the association between $\text{PM}_{2.5}$ exposure and MS progression, many have reported no significant relationships. For example, a Spanish cohort study found no association between PM (PM_{10} and $\text{PM}_{2.5}$) exposure and relapse risk [18]. Similarly, research conducted in Canada found no association with MS incidence [22]. Comparable null findings were reported after adjusting for potential confounders [23], as well as specifically for $\text{PM}_{2.5}$ exposure [24].

In line with the pollutants discussed above, several studies have highlighted a seasonal influence of environmental exposures on MS activity. Short-term exposure to NO_2 (lag 0–3 days) has been linked to relapse occurrence during colder months, whereas O_3 exposure has been associated with relapses in warmer periods [20, 3, 21]. In addition, long-term exposure to NO_2 and SO_2 has been associated with an increased risk of developing MS [4, 8].

However, the overall evidence remains mixed. While some studies report weak correlations involving NO_2 , no significant associations have been observed for CO, O_3 , or other traffic-related pollutants with respect to MS relapse or incidence [21, 24, 18].

Few studies have examined the relationship between weather conditions and MS progression. An increased number of dusty days has been associated with higher MS prevalence, whereas higher average wind speed appears to be linked to reduced prevalence [105]. Increased cloud cover has also been correlated with higher relapse rates, accompanied by reduced levels of global solar radiation [106]. Reduced sunlight exposure has been associated with accelerated disease

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progression [107, 108], while colder climates and lower temperatures have been linked to greater disease incidence and severity [109].

In addition, solar and geomagnetic activity—such as solar flares and geomagnetic storms—may further influence hospital admissions for acute relapses, potentially through indirect effects on atmospheric pressure, temperature, and sunlight exposure [110].

Extreme temperatures, particularly heat, have also been shown to exacerbate MS symptoms. Christogianni et al. [5] highlighted heat as a common and impactful trigger for relapse, with fatigue being the most prominently affected function. Elser et al. [111] observed that individuals with MS are especially vulnerable to abnormally warm weather—an effect expected to intensify with ongoing climate change.

Al et al. [112] reported notable seasonal variation in relapse rates, with the highest frequency occurring during winter months, particularly January and February. However, their study did not identify significant correlations between relapse rates and other meteorological variables, such as humidity, temperature, or rainfall. In contrast, Kadyrova et al. [9] found that low sea-level pressure, often associated with high-altitude environments, may modulate immune function or oxidative stress, thereby potentially influencing MS progression.

Table 2.2 provides a comprehensive overview of the referenced studies, summarizing their reported associations with key air pollutants recognized by the WHO, as well as with relevant weather conditions.

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Table 2.2: Reported correlations between AP and MS outcomes (e.g., progression, relapse, severity)

Exposure	Correlation	No Correlation
PM _{2.5}	[2, 6, 102, 103, 104, 19]	[23, 18, 24]
PM ₁₀	[7, 3, 20, 19, 100, 101]	[23, 18]
NO ₂	[20, 3, 21, 4, 8]	[24, 18]
CO	—	[21]
SO ₂	[4, 8]	—
O ₃	[20, 3, 21]	[24]
Wind Speed	[105]	—
Relative Humidity	—	[112]
Global Radiation	[107, 108, 106, 110]	—
Precipitation	—	[112]
Temperature	[109, 110, 5, 111]	[112]
Sea Level Pressure	[9]	—

2.2.2 Other External Exposures on MS progression

This section examines factors beyond the commonly studied risk variables and environmental influences discussed earlier. These external exposures encompass a broad range of environmental and lifestyle determinants experienced across the lifespan. Together, they provide a more comprehensive perspective on the processes shaping MS progression and management. Incorporating such factors into clinical assessment has the potential to enhance treatment strategies and support more effective disease management.

Smoking increases the risk of MS, heightens disease activity, and accelerates disease progression. Harmful components of tobacco smoke, such as free radicals, cyanates, and carbon monoxide, damage neural tissue, promote brain atrophy, and exacerbate disability [113]. Although smoking cessation cannot reverse existing neurological damage, it has been shown to slow subsequent disability progression to rates comparable to those observed in individuals who have never smoked [114]. Smoking may also serve as an early predictor of conversion from

2.2. Environmental Impact on MS Progression

RRMS to SPMS [115].

Nicotine replacement therapies, including patches and gum, can facilitate smoking cessation and may offer additional neuroprotective benefits. Furthermore, the use of snuff has been associated with slower disease progression compared with conventional cigarette smoking [116].

Interestingly, the *month of birth* has been associated with MS risk [117]. A long-term study involving 2,319 patients in British Columbia reported that individuals born in January had a 40

Obesity has been linked to vitamin D deficiency and is associated with an increased risk of MS [118, 107]. Among patients with RRMS, obesity is associated with greater clinical disability, elevated levels of proinflammatory markers (including IL-6 and leptin), reduced levels of the anti-inflammatory cytokine IL-13, and alterations in lipid profiles that are themselves linked to disability [119]. In addition, obesity has been associated with a higher risk of disease progression in male—but not female—patients [120].

A *brain-healthy lifestyle* has been associated with slower disability progression in MS. Engagement in cognitively and physically stimulating activities, along with the maintenance of a healthy body weight and blood pressure, may reduce the risk of future disability [121]. Specific dietary patterns—including Mediterranean, low-carbohydrate, and fasting-mimicking diets—together with regular *physical activity*, appear to exert beneficial effects on disease progression, particularly when combined with disease-modifying therapies. Among these approaches, the Mediterranean diet and combined exercise training emerge as the most effective and sustainable interventions [122].

2.3 Artificial Intelligence in MS Progression

Early prediction of MS progression, even before clinical manifestations become evident, has become increasingly feasible due to advances in AI. These methods provide powerful tools for both diagnosis and prognosis, with the potential to improve patient outcomes and quality of life. Ensuring interpretability and transparency remains essential for the responsible integration of AI into clinical practice.

This section reviews the application of AI in the investigation of MS progression. Given the rapid expansion of research in this area, representative studies are highlighted that employ AI to predict disease course and model long-term outcomes. For clarity, the review is structured into three subsections: traditional statistical approaches, ML, and DL.

2.3.1 Statistical Approaches to MS Progression

A Gaussian Process (GP) Progression Model (GPPM) applied to individuals with PPMS stratified patients into normative, slow, and fast progressors. Fast progressors were predominantly older males with higher lesion volumes and reached EDSS 6 more rapidly. They exhibited a twofold higher risk of disability progression compared with normative progressors, whereas slow progressors had a 71

Kaplan–Meier and mixed-effects analyses have shown that patients with MS who have existing or incident Cardiovascular Disease (CVD) transition to higher levels of disability significantly faster than those without such comorbidities, underscoring the independent and additive impact of cardiovascular conditions on long-term outcomes [30].

Using longitudinal EDSS changes and brain volume loss within a linear mixed-effects framework, relapses were found to induce temporary increases in disability ($p = 0.012$) but did not predict long-term progression ($p = 0.551$), highlighting the distinction between transient

2.3. Artificial Intelligence in MS Progression

inflammatory effects and irreversible neurodegenerative decline [123].

Using Kaplan–Meier survival curve analysis and Cox proportional hazards models, early disease activity assessed by the Modified Rio Score (MRS) after 12 months of fingolimod treatment was shown to predict long-term disability progression in patients with RRMS. Over a follow-up period of at least three years, patients with higher MRS scores (≥ 2) exhibited an 80% risk of progression, compared with 21.1% among those with lower scores, corresponding to an adjusted hazard ratio of 19.67 [124]. In addition, analyses using a CTMM combined with survival modeling demonstrated that fingolimod slows disability progression in RRMS, with the model capturing both worsening and improvement in clinical status over time [125].

Continuing with Multi-state Model (MSM) approaches, a four-state CTMM applied to more than 6,000 Australian patients found that nearly half of those without initial disability transitioned within one year, with progression rates varying substantially across disease subtypes [126]. An illness–death MSM incorporating hospitalizations and mortality as endpoints showed that early initiation of DMTs reduced hospitalization risk ($HR = 0.79$); however, this benefit declined over time, particularly among patients with fewer comorbidities [29].

Expanding this framework further, a flexible MSM integrating demographic, clinical, and imaging factors across all disease stages demonstrated that higher brain volume was associated with improved recovery probabilities, whereas greater T2 lesion burden and older age increased the risk of disability worsening [127].

Long-term DMT use was initially associated with reduced hospitalization and mortality; however, prolonged treatment paradoxically increased risk in certain subgroups, particularly among patients with fewer comorbidities, as shown using a MSM framework. In contrast, patients with a high comorbidity burden experienced longer survival outside hospital settings [128]. Penalized regression models—including LASSO, ridge, and elastic net—have also been applied to predict dis-

2.3. Artificial Intelligence in MS Progression

ability progression over a two-year horizon, although predictive performance remained modest ($\text{C-index} \leq 0.65$). These findings underscore the difficulty of early-stage forecasting and highlight the need for richer and more informative feature sets [31].

Recent research has increasingly moved beyond simple survival models toward more detailed, time-based approaches, such as CTMMs, which capture dynamic changes in patient status over time. These methods provide a more accurate representation of disease progression and are becoming essential for understanding individual trajectories and informing treatment decisions. More recently, ML has expanded beyond traditional statistical methodologies, offering flexible, data-driven approaches for predicting MS progression, as discussed in the following section.

2.3.2 Machine Learning Methods for Predicting MS Progression

Using clinical and demographic data available at diagnosis, disability worsening has been predicted with the strongest performance achieved by Random Survival Forests (RSF) models ($\text{C-index} = 0.801$), followed by fast kernel Support Vector Machine (SVM) models ($\text{C-index} = 0.690$) [129]. Relapse prediction and transition to SPMS at 6- and 10-year horizons have been modeled using feature selection, Principal Component Analysis (PCA), and multiple classification algorithms, with RF combined with Synthetic Minority Over-sampling Technique (SMOTE) rebalancing achieving the highest accuracy (79%). These findings highlight the value of ensemble-based approaches for long-term risk stratification [130].

Similarly, a framework integrating LASSO-based feature selection with classifiers such as Decision Tree (DT), K Nearest Neighbors (KNN), and SVM has been applied to predict SPMS conversion and

2.3. Artificial Intelligence in MS Progression

disability progression. This approach consistently identified key predictors, including EDSS, relapse history, and age at disease onset; however, F1-scores for conversion remained modest [63].

Temporal dynamics have also been modeled using a regressor chain of RF models to forecast disability levels within time-binned intervals following diagnosis, achieving a Pearson correlation coefficient of 0.72 between predicted and observed outcomes [34].

Logistic regression models have been used to predict disability progression at 6- and 18-month horizons using baseline data, achieving Area Under the Curve (AUC) values of 0.74 and 0.71, respectively, and demonstrating the feasibility of short-term forecasting with minimal input variables [131]. A RF-based model incorporating multimodal data further achieved moderate-to-high predictive accuracy, with omics features providing added value beyond clinical and imaging measures [132]. In addition, gene expression data combined with MRI scans from patients with PPMS were used to predict disability progression and brain volume loss, achieving accuracies of up to 74.1% using RF and SVM models, with further performance gains observed when imaging features were included [32, 133].

Focusing on SPMS, non-parametric models such as RF achieved the highest predictive performance (AUC up to 61.8%), whereas SVM and Linear Regression (LR) performed near chance level. These results support the value of tree-based methods for capturing nonlinear patterns in clinical trial populations [134].

Overall, similar to statistical approaches, ML methods range from simple regression models to advanced ensembles and neural networks, with increasing emphasis on capturing the complex disease dynamics and heterogeneous data modalities underlying MS progression.

2.3.3 Deep Learning for Modeling MS Progression

Early DL approaches employed 3D-Convolutional Neural Network (CNN) architectures to predict disability progression from baseline MRI data, with the inclusion of lesion masks improving predictive performance to an AUC of 0.70 [135]. This model was subsequently applied to early disability prediction, demonstrating superior performance compared with logistic regression and good generalizability across external datasets [136]. More advanced CNN-based frameworks further extended prediction to clinical, cognitive, and combined outcomes, achieving accuracies of up to 85.7

Hybrid architectures, such as hierarchical models combining CNN and Fully Connected Neural Network (FCNN) components, achieved high performance in both lesion segmentation (Dice coefficient = 0.87) and disability classification (91.2% accuracy) [137]. Beyond CNN-based methods, Graph-Based Convolutional Neural Network (GCN)-based models have been shown to outperform traditional 3D-CNNs in disease subtype classification [138], while transfer learning approaches using ResNet50 achieved AUC values ranging from 0.69 to 0.81 for short-term progression prediction [139].

CNN models trained directly on raw T1-weighted MRI scans have been shown to outperform conventional ML approaches based on brain volume features (AUROC = 0.75 vs. 0.62) [140]. Using Optical Coherence Tomography (OCT) data, a FCNN achieved an accuracy of 81.9% for long-term disability prediction over an 8–10-year horizon [141]. For temporal modeling, a Video Vision Transformer (ViViT) architecture demonstrated superior performance compared with CNN-Long Short Term Memory (LSTM) and ViT-LSTM models in 6-year prediction tasks (AUC = 0.84 vs. 0.74), although CNN-LSTM performed better for shorter 2-year forecasts [142].

To summarize, Table 2.3 presents the studies reviewed in this chapter, outlining their primary objectives, methodologies, and key find-

2.3. Artificial Intelligence in MS Progression

ings. A clear trend emerges toward an increasing focus on MS progression in recent years, alongside the expanding application of AI in clinical decision-making and the predominance of ML-based approaches.

Notably, most existing studies concentrate on imaging data or restrict analyses to clinical and demographic features, leaving the integration of environmental exposures into AI-based models of MS progression largely unexplored.

This research addresses this gap by developing comprehensive datasets that integrate clinical, demographic, treatment, and environmental variables to assess the impact of factors such as air pollution and weather conditions on MS progression. The following chapters describe the dataset construction and analytical approaches, with the ultimate goal of evaluating the added value of incorporating environmental exposures into clinical decision-support tools, thereby enabling more personalized management of patients with MS.

2.3. Artificial Intelligence in MS Progression

Table 2.3: Literature review on MS progression

Method Group	Reference Number	Year	Main Aim	Method Used	Result
Statistical Method	[143]	2025	Stratification	GPPM	slow, normative, and fast progressors ($P < 0.0001$)
	[126]	2025	MS progression	CTMM	~50% progressed in 1 year
	[29]	2025	MS hospitality	MSM	HR = 0.79 with DMT
	[127]	2024	Feature Correlation	MSM	Age $\uparrow \Rightarrow$ Risk of worsening $\uparrow$
	[30]	2024	MS progression with CVD	Linear Mixed Effect (LME)	Strong correlation ($p < 0.001$)
	[128]	2024	MS progression	MSM	DMT impact depends on comorbidity
	[132]	2024	MS progression	RF	AUC = 60%
	[31]	2020	MS progression	LASSO, SVM and others	C-index ≤ 0.65
	[123]	2019	Relapse and MS progression	LME	short-term effect ($p = 0.012$)
	[124]	2015	MS progression	KM, Cox PH	HR = 19.67 for $MRS \geq 2$
	[125]	2013	MS progression	CTMM	Positive effect of fingolimod
Machine Learning	[32]	2025	MS progression	Partek Genome Suite [133]	Acc = 74.1 %
	[138]	2024	MS progression	GCN	F1 = 72.2 %
	[129]	2023	Early MS progression	RSF, Fast Kernel SVM	C-indices = 0.801, 0.690
	[33]	2023	MS progression	RSF, Gradient Boosting (GB)	C-index: 0.65 vs. 0.55
	[131]	2023	Disability progression at 6 and 18 months	Logestic regression	AUCs of 0.74 and 0.71
	[34]	2023	MS progression	RF	Pearson $r = 0.72$
	[130]	2022	Relapse prediction	PCA, RF and others	Accuracy = 79 %
	[63]	2020	conversion to SPMS	LASSO, DT, KNN, and SVM	AUC = 0.86 % for a two-year model
	[144]	2020	MS risk	NN	Acc = 64.73 %
	[145]	2019	Remitting vs. non-remitting MS	SVM, DT, RF, NN	Acc = 90.91 %
	[134]	2019	MS progression	RF, SVM, LR	Acc = 61.8 %
	[146]	2020	CIS to MS prediction	RF	Acc = 84.5 %
	[147]	2017	MS worsening (EDSS increase ≥ 1.5)	SVM, LR	Sens = 71 %, Spec = 68 %
	[148]	2015	CIS to MS prediction	SVM	Acc = 71.4 %
Deep Learning	[141]	2024	Long-term disability progression	FCNN	Acc = 81.9 %
	[149]	2024	MS disability stratification	3D-CNN	Acc = 72 %
	[142]	2024	Long-term disability	ViViT, CNN-LSTM	AUC = 0.84
	[136]	2023	early disability	3D-CNN, LR	Acc = 79 %
	[150]	2022	one-year MS progression	DIT	RMSE = 0.68
	[151]	2022	two-year MS progression	CNN	Acc = 85.7 %
	[139]	2022	short-term MS progression	ResNet50	AUC = 81 %
	[135]	2019	one-year MS progression	3D-CNN	AUC = 70 %

Chapter 3

Data Collection, Integration and Preprocessing (Aim 1)

This chapter begins by introducing the datasets employed in this research, starting with the clinical and treatment data, followed by the environmental data, which encompass both air pollution and weather-related variables. The environmental variables are linked to patients through residential postcodes and derived from the nearest monitoring stations. The chapter then describes the construction of the Brain-teaser datasets, with particular emphasis on the processes of data integration and preprocessing, which constituted a substantial portion of the overall effort. Finally, the principal methodological challenges associated with this process are examined, with specific attention given to managing missing data within a longitudinal framework.

3.1 Clinical and Treatment Data Collection from IRCCS Mondino Foundation

The IRCCS Mondino Foundation, an MS center in Pavia, Italy [152], provided the primary dataset for this study, referred to as the *Mondino* dataset. This longitudinal dataset contains multiple clinical observations per patient, collected at irregular time points (i.e., in continuous time). Each patient contributed at least one observation, with some contributing more than 25. The final cohort used for analysis is presented in Figure 3.1.

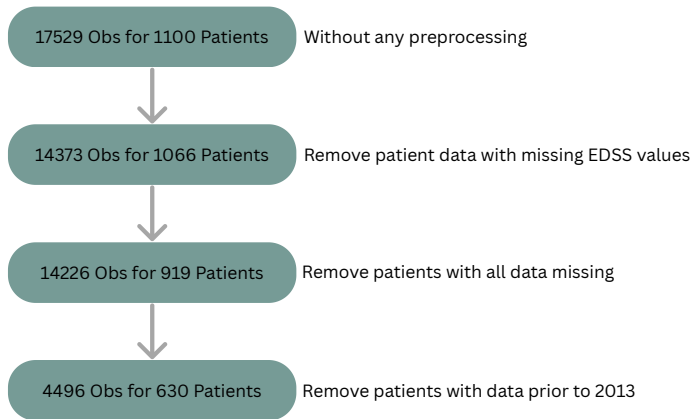


Figure 3.1: Steps in data cleaning and patient inclusion

In longitudinal clinical studies, measurement times often vary across patients. It is uncommon for two individuals to have identical follow-up schedules, as visit timing may depend on disease stage. Longitudinal data are increasingly recognized as essential for improving predictive accuracy and enabling personalized treatment by capturing disease progression and individual clinical trajectories [153, 154] (see

3.1. Clinical and Treatment Data Collection from IRCCS Mondino Foundation

Figure 3.2).

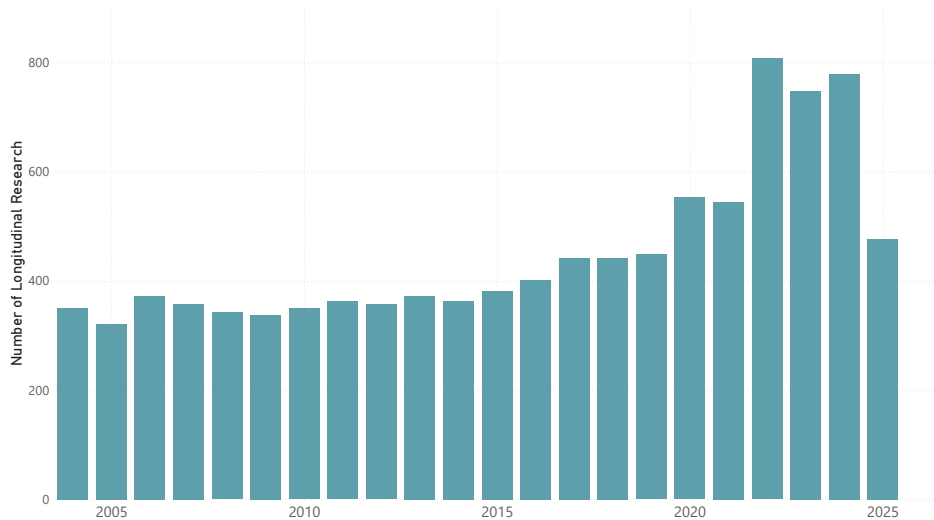


Figure 3.2: Trends in longitudinal research over time

Returning to the dataset, the demographic features include sex, pediatric-onset status, and age, which was recalculated at each visit based on the patient’s date of birth. The clinical component comprises the EDSS score along with eight FS scores: pyramidal, cerebellar, brainstem, visual, mental, sensory, bladder and bowel, and other. These FS scores help distinguish MS-specific neurological impairments from those arising from unrelated conditions, thereby enabling a more precise assessment of disability.

The FS scores were originally developed from clinical observations of 300 patients with MS to capture the core manifestations of the disease, particularly within the pyramidal, cerebellar, brainstem, and sensory systems [64]. Each FS is rated on a scale in which a score of “0” denotes normal neurological function. The maximum score, initially

3.1. Clinical and Treatment Data Collection from IRCCS Mondino Foundation

set at “5,” was revised to “6” in 1965 to better reflect severe impairment; at the same time, the upper limit of the bladder–bowel system was also redefined. The “Other” category differs from the remaining systems in that it is not numerically scaled: a score of “0” indicates absence, whereas a score of “1” denotes the presence of additional neurological findings not captured by the other systems [65].

A relapse count variable was generated for each visit, defined as the number of relapses experienced prior to the visit date. Together with demographic and disability measures, this variable provides a detailed longitudinal clinical profile for each patient. Treatment data were also incorporated, distinguishing between first-line and second-line therapies, as defined by clinicians for managing disease progression. Second-line therapy was initiated when first-line medication proved insufficient. For each patient, the cumulative number of weeks on treatment was calculated.

Figure 3.3 shows the distribution of clinical visits per patient in the Mondino dataset. The distribution is strongly right-skewed: most patients had relatively few visits, while a smaller subset accumulated many more, with some exceeding 35 visits. The majority of patients had fewer than 20 visits, with a peak around 10–15, suggesting moderate follow-up consistent with stable disease or routine care. Beyond 20 visits, the number of patients declines sharply; however, the long tail—extending to nearly 100 visits—likely represents individuals with more complex disease trajectories, frequent relapses, or treatment changes requiring closer clinical monitoring.

Figure 3.4 shows the distribution of time intervals, measured in days, between consecutive clinical visits for the same patient. The distribution is strongly right-skewed, with most intervals shorter than 200 days and a clear peak around 180 days, consistent with the six-month follow-up cycle commonly used in routine MS care. Beyond 200 days, intervals become less frequent, although some exceed 600 days, likely reflecting missed appointments, periods of disease stability, or

3.2. Environmental Exposure Integration from Open-Source Platforms

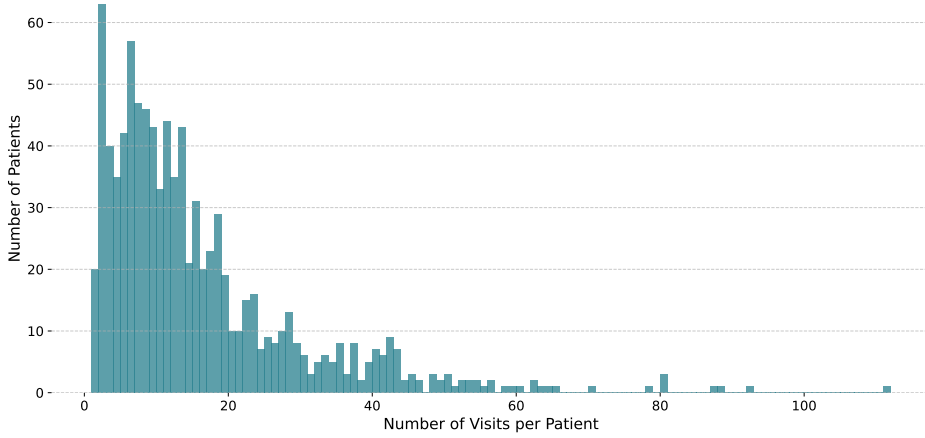


Figure 3.3: Distribution of patient visit frequency

variability in patient adherence and access to healthcare services.

3.2 Environmental Exposure Integration from Open-Source Platforms

Having prepared the clinical dataset as the first component of the integrated data, we now turn to the environmental dataset, which includes air pollution and weather-related variables. The European Environment Agency (EEA) [155] and European Climate Assessment & Dataset (ECAD) [156] were used as the primary sources for Air Quality (AQ) and weather data, respectively. Daily pollutant measurements and gridded weather observations were aligned with each patient’s clinical timeline and residential location to construct the environmental component of the dataset.

3.2. Environmental Exposure Integration from Open-Source Platforms

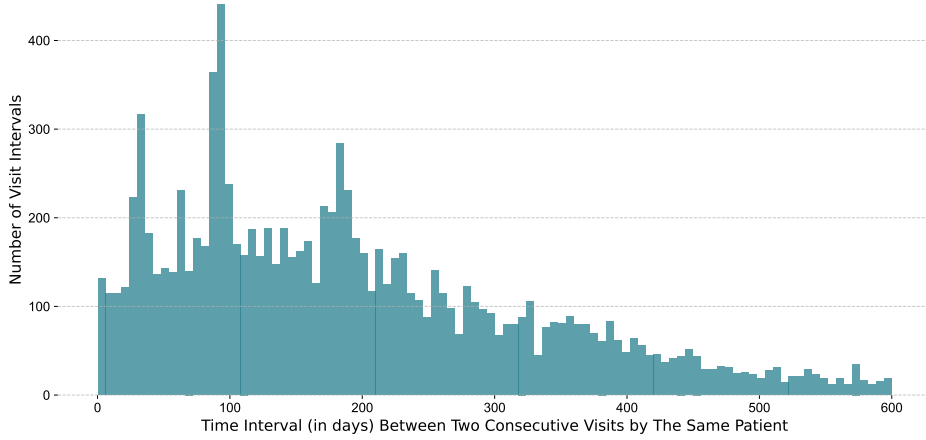


Figure 3.4: Time interval distribution between patient visits

3.2.1 Air Pollution Dataset from European Environment Agency

Macroscale AP data were obtained from public monitoring stations with nationwide coverage. Specifically, datasets were extracted via the DiscoMap interface of the European AQ Portal [157], encompassing official AQ monitoring stations across Italy from January 1, 2013, onward.

The European AQ Portal, managed by the EEA under the AQ e-Reporting initiative of the European Commission (EC), provides tools and services for accessing validated AQ data submitted by EU Member States [158].

Pollutant selection was guided by WHO AQ standards, with a focus on substances associated with well-established health risks: PM (PM₁₀ and PM_{2.5}), SO₂, O₃, NO₂, and CO. Figure 3.5 illustrates the DiscoMap interface used to retrieve pollutant time series, each linked

3.2. Environmental Exposure Integration from Open-Source Platforms

to an individual monitoring station, with detailed metadata available on station location and characteristics.

Country: IT Italy

City name:

Pollutant: PM10

Year from: 2013

Year to: 2021

Source: All

Output type: HTML

Update date:

Time coverage: Year

Update request URL

Download

Figure 3.5: DiscoMap interface for providing AP data

3.2.2 Weather Condition Data from Copernicus

Weather data were obtained from the ECAD through the ENSEMBLES daily gridded observational dataset (E-OBS), which provides climate observations across Europe [156]. The data were downloaded at a spatial resolution of 0.25° (approximately 25 km) and covered the same period as the air pollution data (2013–2022). Provided in Network Common Data Form (NetCDF) format, the files were processed using the NetCDF Python library and contained daily records for key meteorological variables, including wind speed, relative humidity, sea

3.3. Feature Engineering for Environmental Data

level pressure, global radiation, precipitation, and minimum, mean, and maximum temperatures. Each file comprised four dimensions: latitude, longitude, time, and the corresponding measurement values.

To enable integration with patient data, the nearest E-OBS grid points were matched to the air pollution monitoring stations associated with each patient’s residential postcode. Weather and air pollution data were then temporally aligned to produce a unified dataset in matrix form, consisting of five columns: *Id* (unique identifier), *measurement* (weather value), *postcode*, *timestamp*, and *param* (feature name, e.g., mean temperature).

3.3 Feature Engineering for Environmental Data

For each environmental variable, three patient-level summary measures were derived: the average value, the temporal trend, and the exceedance rate relative to WHO AQ guidelines:

- **Mean:** Average of daily values for each environmental variable within the defined time window..
- **Temporal Trend:** Slope of a linear model to daily values within the defined time window.
- **WHO Exceedance Rate:** Proportion of days within the defined time window if pollutant levels exceeded the corresponding WHO thresholds (Table 3.1), calculated as:

$$\text{WHO Exceedance Rate} = \frac{N_x}{T} \quad (3.1)$$

where N_x is the number of days that pollutant x exceeded the WHO threshold during the observation period, and T is the total number of days in that interval.

This approach enabled each patient observation to capture multiple representations of each environmental feature.

3.3. Feature Engineering for Environmental Data

Table 3.1: Recommended AQ guidelines for 24-Hour exposure to common air pollutants

Air Pollutant	Recommended AQ guidelines level
PM ₁₀	$\leq 45 \mu g/m^3$
PM _{2.5}	$\leq 15 \mu g/m^3$
SO ₂	$\leq 40 \mu g/m^3$
O ₃	$\leq 100 \mu g/m^3$
NO ₂	$\leq 25 \mu g/m^3$
CO	$\leq 4 \text{ mg/m}^3$

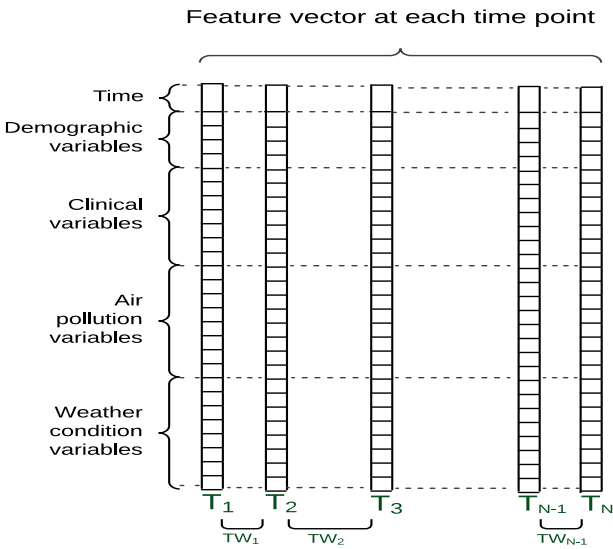


Figure 3.6: Irregular longitudinal record of a patient

3.4 Data Integration

Left-censoring at January 2013 was applied to ensure data completeness, as comprehensive electronic data collection was implemented only from that time onward. Consequently, the first clinical visit occurring after January 2013 was defined as the baseline.

Patients without follow-up after 2013 or with missing postcode information were excluded due to data availability constraints. In addition, patients with more than 40 recorded visits were excluded, as such intensive monitoring typically reflects clinical trial protocols rather than routine clinical practice. Figure 3.7 illustrates the temporal distribution of clinical observations in the original Mondino dataset, highlighting the imbalance between pre- and post-2013 data. Ultimately, approximately 4,500 post-2013 observations, corresponding to about 630 patients, were eligible for linkage with environmental exposure data.

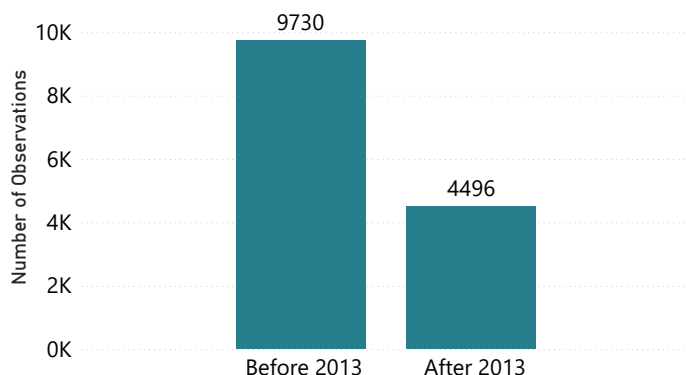


Figure 3.7: Clinical Observation Distribution in the Mondino Dataset

To examine the relationship between environmental exposure and

3.4. Data Integration

disease progression, multiple versions of the integrated dataset were constructed and organized into two categories—*short-term* and *long-term*—as illustrated in Figure 3.8.

- In the *short-term* dataset, environmental exposure was summarized by averaging feature values over time windows ranging from 1 to 5 weeks before each clinical visit.
- In the *long-term* dataset, environmental exposure was calculated over one of three intervals: the 6 months preceding a visit, the 1 year preceding a visit, or the entire period between two consecutive clinical visits. For baseline visits, where no prior record existed, exposure was assessed using data from the 180 days before the visit date—also the default interval set by clinicians for patient follow-up.

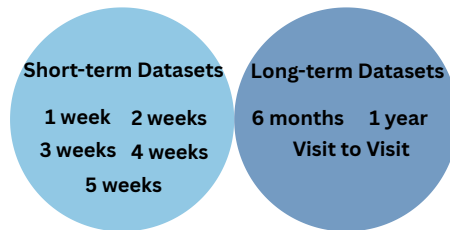


Figure 3.8: The Integrated datasets created in this research

In the *visit-to-visit* dataset, each row corresponds to a unique time window for an individual patient. The duration of these windows and the number of follow-up visits vary across patients, reflecting the irregular nature of longitudinal data.

Each dataset includes three demographic features, ten clinical variables, two treatment-related factors, and 34 environmental attributes—comprising 18 air pollution measures (mean, temporal trend, and WHO exceedance rate) and 16 weather-related metrics.

3.5. Handling Missing Longitudinal Data; Clinical and Environmental Data

To illustrate this structure, Figure 3.6 depicts the temporal framework used in the analysis. Patient data are organized into irregularly spaced time points, $T = (T_1, \dots, T_N)$, where each T_i denotes a clinical visit. These are then grouped into time-windowed sequences, $TW = (TW_1, \dots, TW_N)$, capturing the dynamic evolution of the disease over time.

3.5 Handling Missing Longitudinal Data; Clinical and Environmental Data

Missing data pose a challenge in all empirical studies, including longitudinal research, and commonly arise from missed appointments, incomplete documentation, or technical issues during data collection [159, 160]. Simply omitting incomplete records can lead to substantial data loss—an issue that is particularly critical in the context of MS, where data collection is time-intensive and resource-demanding [161, 162, 163]. To mitigate these limitations, imputation methods specifically designed for longitudinal data are essential [162].

In recent years, only a limited number of advanced imputation strategies have been proposed to address missingness in longitudinal clinical data. Luo et al. [159] introduced 3D-Multiple Imputation with Chained Equations (MICE), which integrates MICE with GP modeling and demonstrated superior performance compared with either method alone, achieving an Root Mean Square Error (RMSE) of 0.342. Huque et al. [164] conducted a large-scale evaluation of 12 Multiple Imputation (MI) techniques, showing that Standard Fully Conditional Specification (FCS Standard) and Joint Multivariate Normal Imputation (JM MVN) produced less biased estimates and improved regression parameter coverage. Daberdaku et al. [165] proposed a hybrid approach combining linear interpolation with weighted KNN for

3.5. Handling Missing Longitudinal Data; Clinical and Environmental Data

imputing longitudinal laboratory data from Intensive Care Unit (ICU) settings.

In the present study, missing values were observed in both the clinical and environmental datasets. For the environmental data, a small number of air quality monitoring stations lacked daily measurements during the study period. These missing values were imputed using the Inverse Distance Weighting (IDW) method [166], which estimates values as weighted averages of measurements from nearby stations within a 50 km radius, assigning greater weight to closer stations.

In the clinical dataset, approximately 2,000 records in the *Mondino* dataset contained at least one missing FS score (Table 3.2). An initial pool of 14 imputation methods was evaluated, from which the five most accurate approaches were selected for further analysis. These selected methods fall into three categories: *single imputation*, *MI*, and *Joint Modelling (JM)*, with the latter evaluated at both clustered and single-patient levels.

Table 3.2: Proportion of missing data in FS scores

Feature Name	Missing rate (%)
Pyramidal	11.28
Cerebellar	13.27
Brainstem	13.22
Sensitive	12.77
Bladder and Bowel	13.53
Visual	13.70
Mental	13.84
Other	14.73

Single imputation methods include Linear interpolation, Spline interpolation, Last Observation Carried Forward (LOCF), and Expo-

3.5. Handling Missing Longitudinal Data; Clinical and Environmental Data

nentially Weighted Moving Average (EWMA). Linear interpolation [167] estimates missing values by connecting adjacent observed points with straight lines while spline interpolation [168] fits smooth polynomial curves, allowing nonlinear trends to be captured. LOCF [169] replaces missing values with the most recent observed measurement for a patient. Finally, EWMA [170] applies exponentially decaying weights to surrounding time points (e.g., $t - 1, t - 2, t + 1, t + 2$) to generate estimates, making it particularly useful in time series with temporal dependencies. The imputed value at time t is given by:

$$\hat{x}_t = \frac{\sum_{i=0}^k \lambda^i x_{t-i}}{\sum_{i=0}^k \lambda^i} \quad (3.2)$$

with a weighting factor of $\lambda = 0.5$ and a window length of $k = 2$. MI generates multiple plausible datasets by drawing values from a predictive distribution, analyzing each dataset separately, and then pooling the results to account for imputation uncertainty. A variety of MI techniques have been employed in the literature, including Predictive Mean Matching (PMM) [171], Classification and Regression Tree (CART) [172], Bayesian Linear Regression (BLG) [173], RF, and variants of LR [174].

In contrast, JM assumes multivariate normality and preserves inter-variable correlations by imputing missing values through a joint modeling framework. This approach employs Gibbs sampling with a Metropolis–Hastings step to update the covariance matrix and is implemented in the Jomo package [175].

Imputation was performed using data from the same patient only. To evaluate imputation accuracy, artificial missingness was introduced by randomly removing values from complete cases (approximately 12,000 observations from more than 800 patients), and performance was assessed using the RMSE. While MI methods typically pool results across multiple completed datasets [176], the objective of this

3.5. Handling Missing Longitudinal Data; Clinical and Environmental Data

study was to generate a single reliable and complete dataset to serve as the foundation for subsequent predictive modeling.

Table 3.3 summarizes imputation performance under a 10% missingness scenario. Unexpectedly, linear interpolation and EWMA achieved the lowest RMSE values, outperforming both MI and JM approaches. The strong performance of EWMA further confirms its effectiveness in time-series analysis, as the use of exponentially decaying weights enables improved preservation of temporal dynamics.

Among the MI methods, tree-based approaches such as CART and RF demonstrated the strongest performance. Notably, model complexity had little influence on the results: RF with ten trees performed comparably to CART with a single tree. In contrast, MI approaches based on LR variants generally yielded weaker performance; however, LGnob (LR without parameter uncertainty) produced acceptable results. Within the JM category, clustered-level imputation outperformed single-level approaches, likely reflecting the inherently hierarchical structure of longitudinal data.

These findings suggest that patterns within the dataset exhibit relatively smooth within-patient time series, with few abrupt fluctuations between visits. At the same time, relationships between variables can be well approximated by underlying linear patterns with relatively stable coefficients. Together, these characteristics help explain why interpolation-based methods such as linear interpolation and EWMA achieved strong performance, as they effectively leverage both gradual within-patient temporal dynamics and stable between-variable associations.

Accordingly, EWMA was selected as the primary imputation method for subsequent analyses. Three strategies were evaluated: (1) mean imputation followed by LME, (2) EWMA combined with LME, and (3) standalone EWMA using the same configuration as before. The LME model [177] extends linear regression by incorporating both fixed effects (shared across individuals) and random effects (individual-specific),

3.5. Handling Missing Longitudinal Data; Clinical and Environmental Data

Table 3.3: Imputation method performance (Study 1)

Imputation Group	Method	RMSE
Single Imputation	Linear	0.48
	Spline	0.62
	LOCF	0.61
	EWMA	0.47
Multiple Imputation	PMM	0.69
	CART	0.55
	RF	0.57
	BLG	0.76
	LG	0.96
	LGP	0.62
	LGnob	0.75
Joint Modelling	JM Clustered-Level data	0.60
	JM Single-Level data	0.75
	JM LG	0.76

making it particularly well suited for longitudinal data. By including subject-level random effects, LME accounts for within-subject correlation across repeated measurements.

Let $y_i = (y_{i1}, y_{i2}, \dots, y_{in_i})^T$ be the n_i repeated measurements of the response variable for individual i , where $i = 1, 2, \dots, n$. The general LME model is defined as:

$$\begin{aligned}
 y_i &= X_i\beta + Z_ib_i + e_i \\
 b_i &\sim \mathcal{N}(0, D) \\
 e_i|b_i &\sim \mathcal{N}(0, R_i)
 \end{aligned} \tag{3.3}$$

Here, $\beta = (\beta_1, \dots, \beta_p)^T$ is a $p \times 1$ vector of fixed effects, $b_i = (b_{i1}, \dots, b_{iq})^T$ is a $q \times 1$ vector of random effects, $e_i = (e_{i1}, \dots, e_{in_i})^T$ represents the random error for repeated measures, D is the $q \times q$

3.6. Optimal Imputation–Prediction Pairing with Traditional ML Models

covariance matrix of the random effects, and R_i is the $n_i \times n_i$ covariance matrix of residuals for subject i .

The results presented in Table 3.4 demonstrate that the EWMA+LME approach consistently outperforms all other methods across varying levels of missingness, underscoring the advantage of combining temporal smoothing with subject-specific structural modeling. Although the Mean+LME strategy yields slightly higher error rates, its performance remains competitive, further highlighting the ability of the LME framework to capture the underlying dynamics of longitudinal clinical data. In contrast, the standalone EWMA method exhibits a marked increase in error as the degree of missingness intensifies, suggesting that the incorporation of patient-level random effects is crucial for achieving robust imputation under conditions of incomplete observation.

Table 3.4: Imputation performance by missing rates (Study 3)

Imputation Method	Missing Rate (%)				
	10	20	30	40	50
EWMA + LME	0.2264	0.3280	0.4046	0.4679	0.5320
Mean + LME	0.2269	0.3283	0.4049	0.4683	0.5330
EWMA	0.2814	0.4121	0.5123	0.5960	0.6775

3.6 Optimal Imputation–Prediction Pairing with Traditional ML Models

To evaluate the impact of imputation on predictive performance, imputation–prediction pipelines were constructed using a range of methods, excluding LME-based approaches. Several traditional ML models were employed, including KNN [178], Light Gradient Boost-

3.6. Optimal Imputation–Prediction Pairing with Traditional ML Models

ing Machine (LightGBM) [179], RF [180], and SVM [181], representing neighbor-based, ensemble-based, and kernel-based learning paradigms. Model performance was evaluated using the coefficient of determination (R^2) defined as:

$$R^2 = 1 - \frac{SSR}{SS_t} \quad (3.4)$$

where SSR denotes the sum of squared residuals and SS_t the total sum of squares, defined as the squared deviations of the observed values from their mean. The incomplete longitudinal dataset was partitioned into training (80%) and test (20%) sets. Patient identifiers were used to ensure that all observations belonging to a given individual were assigned exclusively to one set, thereby preventing data leakage.

A 10-fold Cross Validation (CV) procedure combined with grid search was employed to identify optimal imputation–prediction combinations and corresponding hyperparameters. All possible method pairs were systematically evaluated within each fold, and the average R^2 across folds was computed. The five top-performing combinations were then retained and applied to the test set, where missing values were imputed and outcome predictions were generated.

Table 3.5 reports performance results on both the training and test sets. The CART–SVM combination achieved the highest R^2 values, with 0.891 on the training set and 0.725 on the test set, demonstrating strong predictive accuracy and good generalization. Moreover, CART-based imputation consistently yielded high training performance across other predictive models, including RF (0.887), LightGBM (0.881), and KNN (0.830), outperforming all alternative imputation strategies.

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3.6. Optimal Imputation–Prediction Pairing with Traditional ML Models

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In terms of predictive robustness, RF consistently demonstrated strong performance across different imputation strategies. For example, when combined with linear interpolation, it achieved R^2 values of 0.742 on the training set and 0.688 on the test set, whereas when paired with EWMA, performance was slightly lower, with R^2 scores of 0.715 (training) and 0.673 (test). Even when combined with clustered-level JM, RF maintained competitive performance, reaching R^2 values of 0.720 on the training set and 0.622 on the test set. These findings underscore the robustness of RF to variations in imputation strategy and its strong capacity for generalization.

The SVM model also demonstrated strong predictive capability when paired with high-quality imputed data. Beyond its top performance when combined with CART-based imputation, it achieved a notable test-set R^2 of 0.709 when paired with RF imputation, confirming that accurate prediction is highly dependent on well-prepared input data.

In contrast, KNN and LightGBM exhibited greater variability in performance, with results strongly influenced by the choice of imputation method. Across all predictive models, CART emerged as the most effective imputation strategy, consistently enhancing downstream predictive performance. Although EWMA and linear interpolation

3.6. Optimal Imputation–Prediction Pairing with Traditional ML Models

Table 3.5: Performance of the imputation–prediction pairs

Imputation Method	Prediction Model	R^2 (Train)	R^2 (Test)
Linear	KNN	0.621	–
	LightGBM	0.715	–
	RF	0.742	0.688
	SVM	0.720	–
EWMA	KNN	0.616	–
	LightGBM	0.696	–
	RF	0.715	0.673
	SVM	0.710	–
CART	KNN	0.830	–
	LightGBM	0.881	–
	RF	0.887	–
	SVM	0.891	0.725
RF	KNN	0.799	–
	LightGBM	0.848	–
	RF	0.855	–
	SVM	0.856	0.709
JM Clustered-Level Data	KNN	0.628	–
	LightGBM	0.706	–
	RF	0.720	0.622
	SVM	0.698	–

achieved the lowest RMSE values in the standalone imputation evaluation, their effectiveness diminished when embedded within the prediction pipeline. Among these approaches, the best-performing combination was linear interpolation with RF, which achieved R^2 scores

3.6. Optimal Imputation–Prediction Pairing with Traditional ML Models

of 0.742 (training) and 0.688 (test).

Finally, JM, particularly the clustered-level variant, produced acceptable but suboptimal predictive results. While these findings highlight the suitability of JM for hierarchical or multilevel data structures, its predictive performance remained inferior to that of tree-based imputation methods.

In summary, Figure 3.9 illustrates the integration and preprocessing workflow applied to the combined datasets. This chapter introduced the clinical and environmental datasets used in this study and detailed the procedures employed for their integration and preprocessing. Both short-term and long-term variants of the integrated dataset were constructed, and missing values in clinical and environmental features were addressed using multiple imputation strategies, whose impact was subsequently evaluated through predictive modeling.

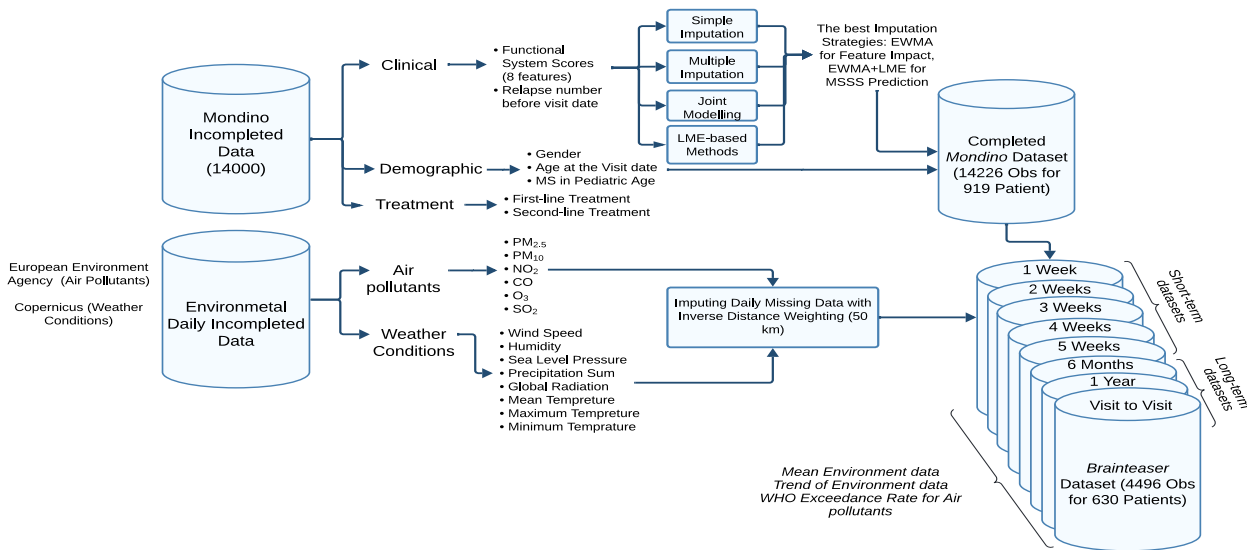


Figure 3.9: Data integration and preprocessing steps

Chapter 4

Feature Impact Analysis on MS Progression (Aim 2)

Understanding the association between environmental exposures and MS progression is essential for guiding targeted interventions and improving predictive models. [9]. CTMM, a memoryless discrete-state stochastic process, models transitions between disease states in continuous time. It is particularly suited to chronic conditions such as MS, where follow-up visits occur at irregular intervals, and enables estimation of how covariates influence disease progression rates [182]. While the analysis considers a broad range of demographic and clinical variables, particular emphasis is placed on AP and weather conditions. To the best of our knowledge, this is the first study to examine the combined impact of these factors on MS progression within this modeling framework.

4.1 Continuous-Time MS Dataset

The short- and long-term datasets, comprising five and three variants respectively, were used in this analysis. To maintain focus on the most informative outcomes, only the best-performing dataset from each category is reported. For the short-term analysis, the 5-week window preceding each clinical visit was selected, whereas for the long-term analysis, the interval between consecutive visits yielded the best results. Consistent with the imputation performance, both datasets were constructed using the EWMA method, although a different imputation strategy will be adopted in the following chapter.

4.2 Data Preprocessing Pipeline for Feature Impact Analysis

To model MS progression using a CTMM, several preprocessing steps were applied, as illustrated in Figure 4.1. Although patients with only a single observation had already been removed at earlier stages, the integration of clinical and environmental datasets revealed additional single-observation cases, which were subsequently excluded.

After careful consideration, the EDSS scores were stratified into three clinically meaningful and model-optimal states: (1) very mild (0–1), (2) mild (1.5–2.5), and (3) moderate-to-severe (> 2.5). The choice of thresholds and the number of states was guided by several factors: (i) the frequency of observed transitions, (ii) the initial transition probabilities, (iii) the covariates included in the model, and (iv) the model hyperparameters. Each of these factors required careful tuning across both datasets.

As shown in the figures, model convergence was not always guaranteed. Whenever convergence failures or numerical instabilities (e.g., overflows) emerged as a consequence of the chosen state definitions

4.2. Data Preprocessing Pipeline for Feature Impact Analysis

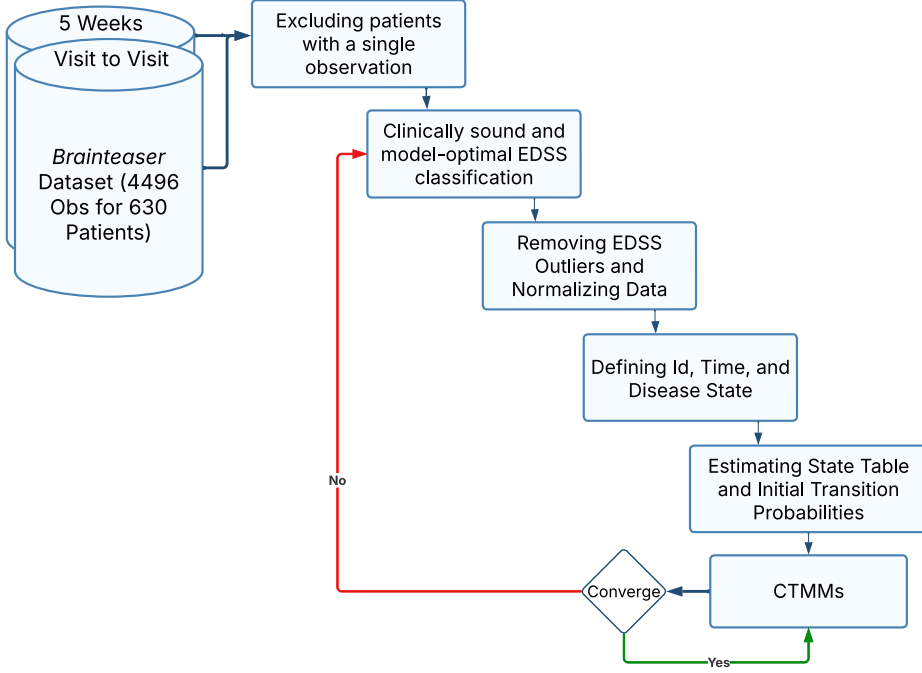


Figure 4.1: Data preparation for a CTMM model

or modeling parameters, the class boundaries were systematically adjusted and the models were re-estimated to ensure numerical stability. This iterative process was repeated until a set of EDSS classes was identified that balanced clinical interpretability with model stability.

Outlier EDSS values were removed and the dataset was then normalized using z-score transformation. With three essential components seen in each observation row (patient identifier, visit date, and the corresponding disease state), the state transition table and initial transition probability matrix (Q) were estimated. It is an $n \times n$ matrix, where n represents the number of defined disease states. Each

4.3. MS Progression Modeling with CTMM

off-diagonal element λ_{ij} in the matrix denotes the instantaneous rate of transition from state i to state j , and these values are derived from the state table.

Finally, the model was trained on both datasets comprising 4196 observations from 585 patients. Table 4.1 provides a detailed summary of the final dataset, which includes data from five weeks prior to the visit date. Among the temperature-related variables, only mean temperature was retained for this analysis.

4.3 MS Progression Modeling with CTMM

While survival analysis is widely used to evaluate the effects of covariates, it has several key limitations when applied to modeling MS progression. In particular, it assumes unidirectional worsening and cannot accommodate improvements, focuses on a single event rather than repeated episodes, and treats all disability transitions equivalently (e.g., transitions from EDSS 1 to 2 versus from 3 to 5). These limitations render time-to-event models unsuitable for the objectives of this study [182].

In contrast, Markov models overcome these constraints by allowing both deterioration and improvement between disease states, while flexibly incorporating covariates to estimate their effects on specific transitions. These models rely on the Markov assumption, whereby the future state depends only on the current state and not on the full history of prior states. As the primary aim of this study is to identify factors influencing disease progression, the analysis focuses on modeling such state transitions.

Markov models can be formulated in either discrete time, with transitions occurring at fixed intervals, or continuous time, where transitions may occur at any moment. In the present study, a continuous-time formulation was adopted and applied to two datasets to examine

4.3. MS Progression Modeling with CTMM

how different covariates influence disease progression under varying data conditions [183, 184].

4.3. MS Progression Modeling with CTMM

Table 4.1: Summary of patient demographic, clinical, and environmental variables, grouped by EDSS. Descriptive statistics are presented as count (percentage), mean (min-max), mean $\pm$ standard deviation, or median (min-max).

Feature	Total	Very Mild	Mild	Moderate-to-Severe
Patients	585	209	240	136
EDSS	1.5 (0–8.5)	1 (0–1)	2 (1.5–2.5)	6 (3–8.5)
Demographic				
Sex at birth (Female)	394 (67%)	141 (35%)	170 (43%)	83 (21%)
MS in Pediatric Age (Yes)	31 (5.2%)	9 (4.3%)	16 (6.6%)	6 (4.4%)
Age	41.9 $\pm$ 11.74	36.04 $\pm$ 9.60	40.1 $\pm$ 10.75	51.04 $\pm$ 10.30
Clinical				
Pyramidal	1 (0–6)	1 (0–5)	1 (0–5)	2 (0–6)
Cerebellar	0 (0–9)	0 (0–4)	0 (0–4)	1 (0–9)
Brain Stem	0 (0–5)	0 (0–3)	0 (0–4)	1 (0–5)
Sensory	1 (0–5)	0 (0–3)	1 (0–3)	2 (0–5)
Bladder & Bowel	0 (0–3)	0 (0–3)	0 (0–6)	0 (0–5)
Visual	0 (0–9)	0 (0–5)	0 (0–4)	0 (0–9)
Mental	0 (0–4)	0 (0–2)	0 (0–3)	0 (0–4)
Other	0 (0–13)	0 (0–6)	0 (0–10)	0 (0–13)
Relapse Number	3 (0–47)	2 (0–18)	3 (0–44)	5 (0–47)
First-line Treatment	0 (0–5)	0 (0–5)	0 (0–5)	0 (0–5)
Second-line Treatment	0 (0–5)	0 (0–5)	0 (0–5)	0 (0–5)
Environment				
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	31.56 $\pm$ 13.01	31.70 $\pm$ 13.19	31.55 $\pm$ 12.91	31.45 $\pm$ 12.96
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	22.08 $\pm$ 11.11	22.20 $\pm$ 11.40	22.20 $\pm$ 11.05	21.79 $\pm$ 1.84
SO ₂ ($\mu\text{g}/\text{m}^3$)	4.65 $\pm$ 1.91	4.51 $\pm$ 1.98	4.72 $\pm$ 1.86	4.70 $\pm$ 1.88
O ₃ ($\mu\text{g}/\text{m}^3$)	46.20 $\pm$ 27.24	45.93 $\pm$ 27.30	45.78 $\pm$ 27.04	47.25 $\pm$ 27.50
NO ₂ ($\mu\text{g}/\text{m}^3$)	30.78 $\pm$ 12.63	31.19 $\pm$ 12.92	30.83 $\pm$ 12.51	30.15 $\pm$ 12.46
CO (mg/m ³)	0.61 $\pm$ 0.25	0.63 $\pm$ 0.26	0.61 $\pm$ 0.25	0.60 $\pm$ 0.24
Wind Speed (m/s)	2.33 $\pm$ 0.39	2.32 $\pm$ 0.38	2.33 $\pm$ 0.40	2.34 $\pm$ 0.40
Relative Humidity (&)	69.03 $\pm$ 7.46	69.21 $\pm$ 7.51	69.07 $\pm$ 7.42	68.75 $\pm$ 7.44
Global Radiation (W/m ²)	151.48 $\pm$ 77.67	150.89 $\pm$ 77.24	150.26 $\pm$ 77.96	154.32 $\pm$ 77.78
Precipitation (mm)	2.27 $\pm$ 1.63	2.31 $\pm$ 1.68	2.23 $\pm$ 1.57	2.28 $\pm$ 1.67
Mean Temperature (°C)	13.55 $\pm$ 7.37	13.64 $\pm$ 7.35	13.34 $\pm$ 7.43	13.80 $\pm$ 7.32
Sea Level Pressure (hPa)	1015.89 $\pm$ 4.78	1015.79 $\pm$ 5.26	1015.99 $\pm$ 4.61	1015.86 $\pm$ 4.38

4.3. MS Progression Modeling with CTMM

Consider a longitudinal dataset where M denotes the number of subjects, and N_m is the number of observations at irregular times for the m^{th} subject. Each subject can move among $S = \{1, 2, \dots, S\}$ states. The time of the k^{th} observation for subject m is denoted by t_{mk} , and the subject's state at that time is $s_{mk} \in S$. Let $S(t) = i$ denote the state of subject m at time t_{mk} . Then, the transition intensity with which the subject moves to state j during the time interval $(t + \Delta t)$ is defined as: The transition intensity with which the subject moves to state j during the time interval $(t + \Delta t)$ is defined as:

$$\lambda_{ij} = \lim_{\Delta t \rightarrow 0} \frac{P(S(t + \Delta t) = j \mid S(t) = i)}{\Delta t} \quad (4.1)$$

The schematic diagram represented in Figure 4.2 for the MS progression states offers the following transition intensity matrix:

$$Q = \begin{bmatrix} -(\lambda_{12} + \lambda_{13}) & \lambda_{12} & \lambda_{13} \\ \lambda_{21} & -(\lambda_{21} + \lambda_{23}) & \lambda_{23} \\ \lambda_{31} & \lambda_{32} & -(\lambda_{31} + \lambda_{32}) \end{bmatrix} \quad (4.2)$$

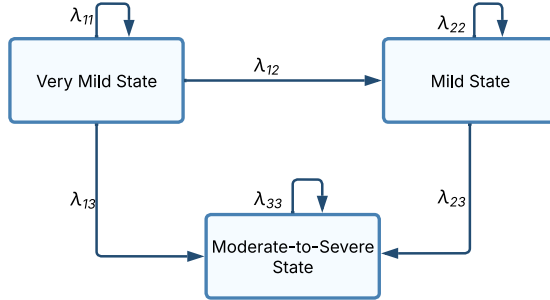


Figure 4.2: Multistate model for MS progression

λ_{ij} denotes the instantaneous rate of transition from state i to state j . The matrix Q must satisfy the following two important properties:

4.3. MS Progression Modeling with CTMM

1. The sum of the elements in each row of Q is zero:

$$\sum_j \lambda_{ij} = 0$$

2. The diagonal elements are defined as the negative sum of the off-diagonal elements in the same row:

$$\lambda_{ii} = - \sum_{j \neq i} \lambda_{ij} \quad (4.3)$$

It is assumed that the observation time points are ordered and that the disease states follow a first-order continuous-time Markov process with a finite number of discrete states, as defined in Equation (4.4).

$$\Pr(s_{mk} \mid s_{m(k-1)}, s_{m(k-2)}, \dots, s_{m1}) = \Pr(s_{mk} \mid s_{m(k-1)}) \quad (4.4)$$

The probability of the m^{th} subject transitioning from state i at time $t_{m(k-1)}$ to state j at time t_{mk} is denoted as:

$$p_{ij}(t_{m(k-1)}, t_{mk}) = \Pr(s_{mk} = j \mid s_{m(k-1)} = i) \quad (4.5)$$

Table 4.2 presents the state transition table for disease progression in the datasets analyzed in this study, indicating that most patients remained in the same disease state over several years of follow-up. The model was implemented using the `msm` package in R [185].

4.3. MS Progression Modeling with CTMM

Table 4.2: State transition table of MS progression

	Very Mild	Mild	Moderate-to-Severe
Very Mild	1049	104	7
Mild	84	1418	53
Moderate-to-Severe	7	36	315

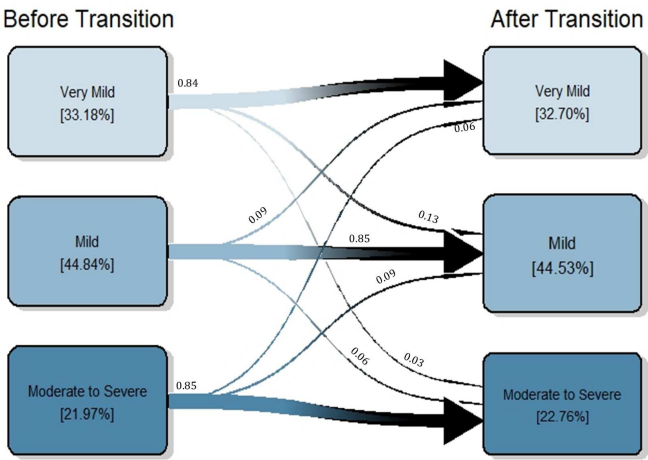


Figure 4.3: Transitions diagram for MS progression States

As shown in Figure 4.3, the proportion of patients in the mild state (state 2) remains higher than in the other two states, both before and after transitions. This pattern is consistent with the results reported in Table 4.2, which confirm a strong tendency for patients to remain in the same disease state across transitions. Notably, the probability of transitioning from the mild state to the very mild state is higher than that of progressing to the moderate-to-severe state, potentially reflecting the beneficial effects of treatment over time in patients with MS. Nevertheless, the number of patients in the moderate-to-severe

4.3. MS Progression Modeling with CTMM

state (state 3) increases following transitions, indicating that disease progression persists for a subset of individuals despite treatment.

The fit of multiple Markov models incorporating different sets of covariates was evaluated using the normalized $-2 \times \log(\text{Likelihood})$ criterion, scaled by a factor of 1,000 for readability. This likelihood-based metric is widely used for model comparison and facilitates assessment of how effectively each model captures the underlying structure of the data. Lower values of $-2 \times \log(\text{Likelihood})$ indicate superior model fit.

The following sections examine the influence of covariates on MS progression using the Hazard Ratio (HR) as a measure of relative risk. An HR of 1 indicates no effect on progression within the specified time frame (here, per week). Values greater than 1 correspond to an increased risk of transitioning to a worse disease state, whereas values less than 1 suggest a protective effect or reduced risk. For example, an HR of 1.2 represents a 20% higher likelihood of progression, while an HR of 0.8 reflects a 20% reduction in risk.

4.3.1 Impact of Clinical and Demographic Features on MS Progression

This section reports the effects of clinical, demographic, and treatment-related features on MS progression, with a particular focus on two key transitions: from very mild to mild disability and from mild to moderate-to-severe disability. Clinical and demographic factors, which were consistent across both the short- and long-term datasets, were evaluated using the short-term dataset. Treatment-related features were assessed in both datasets to capture potential temporal effects. All results were obtained from one-covariate models, in which each of the 14 covariates was analyzed independently.

Beginning with demographic factors, Figure 4.4 illustrates that

4.3. MS Progression Modeling with CTMM

age plays a significant role in MS progression. Specifically, older patients exhibit a higher likelihood of transitioning to more severe disease stages, consistent with previous findings reported by Zeydan et al. [186].

4.3. MS Progression Modeling with CTMM

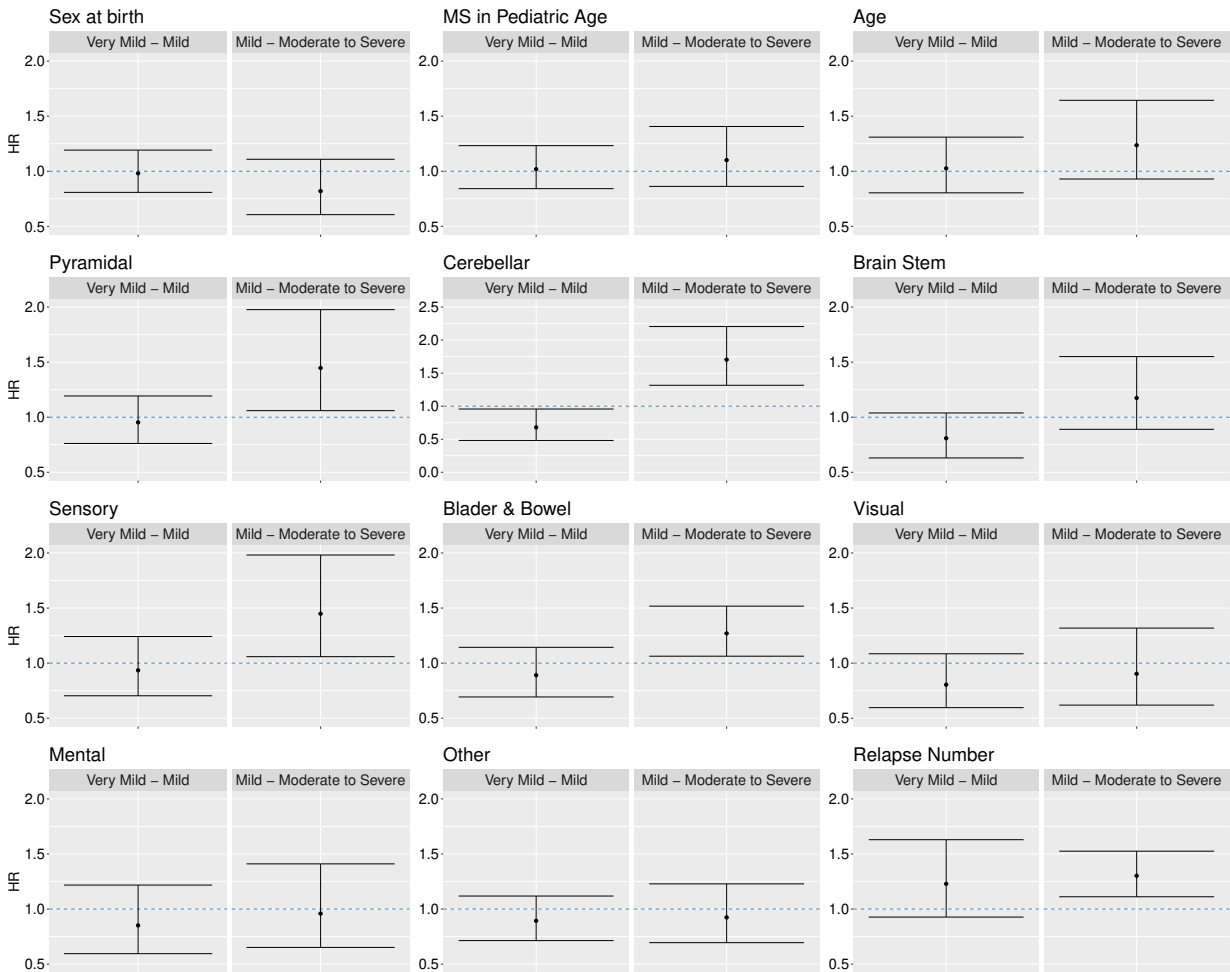


Figure 4.4: Estimated hazard ratios of demographic and clinical features on EDSS state progression transition (error bars show 95% confidence intervals)

The findings become particularly compelling when examining the FS scores, which show a strong association with MS progression across

4.3. MS Progression Modeling with CTMM

both transitions. Among these, the pyramidal, cerebellar, sensory, bladder and bowel, and relapse number scores exert the most substantial influence, particularly in the more advanced stages of the disease. In practical terms, deterioration in these functional domains markedly increases the likelihood of progression, whereas stability or improvement may contribute to slowing disease worsening.

The cerebellar score emerges as especially noteworthy. Although cerebellar impairments have a limited impact during the earliest stages, their influence on progression becomes considerably more pronounced at later stages of the disease. A similar, albeit weaker, pattern is observed for the brainstem and bladder and bowel scores. In contrast, the visual, mental, and “other” scores consistently exhibit the weakest associations with progression.

The relapse number is also consistent with established clinical evidence [187], confirming that patients experiencing a higher number of relapses face an increased risk of disease worsening. Notably, the results suggest that this effect is less pronounced in the early stages but intensifies as the disease advances.

Overall, these findings indicate that not all FS scores are equally informative predictors of MS progression. Particular emphasis should be placed on pyramidal, cerebellar, sensory, brainstem, and bladder and bowel scores, as well as relapse frequency, especially in patients who have already reached more advanced disease stages ($\text{EDSS} \geq 1$).

When evaluating the impact of first-line treatment across both short- and long-term periods (Figure 4.5), no statistically significant differences were observed in disease state transitions overall. However, during the early stage of the disease, long-term first-line treatment appeared to stabilize or even improve disease status, with no progression detected. This pattern is consistent with the *Progression* outcome introduced in Chapter 2, where improvements outweigh progression events.

In later stages, particularly during the transition from mild to

4.3. MS Progression Modeling with CTMM

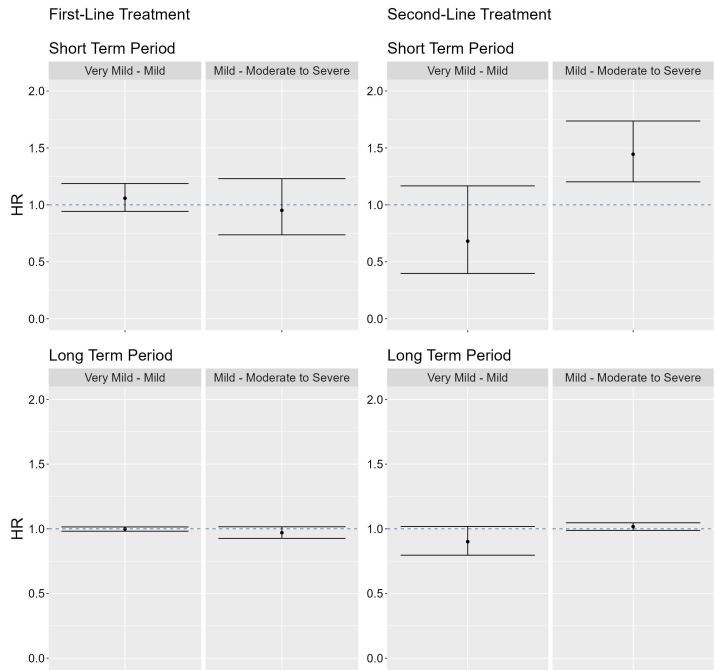


Figure 4.5: Estimated hazard ratios of treatment features on EDSS state progression transition (error bars show 95% confidence intervals)

moderate-to-severe disability, first-line treatment was associated with a reduced long-term risk of progression. These findings suggest that, in MS, first-line therapies may require sustained and continuous use to achieve their full clinical benefit, underscoring the importance of long-term treatment adherence [188]. Moreover, these results support the appropriateness of treatment timing at the clinical center from which the data were collected, indicating that early and consistent intervention can be effective in controlling disease activity during its initial stages.

In contrast, a different pattern emerged for second-line treatment.

4.3. MS Progression Modeling with CTMM

In the short term, the HR for the transition from mild to moderate-to-severe disability exceeded 1, suggesting an apparent increased risk of progression. However, this finding should not be interpreted as a detrimental treatment effect. Two alternative explanations are more plausible: (i) second-line treatment is often initiated at a relatively advanced disease stage, when disease control is already compromised; or (ii) the short observation window may be insufficient to capture the full therapeutic benefit. Long-term analyses support these interpretations, as the corresponding HR approached 1, indicating no significant long-term effect on progression.

Notably, the short-term pattern suggests that second-line therapies are frequently introduced too late in the disease course and that earlier initiation may lead to improved outcomes. Interestingly, over the long term, second-line treatment appeared to reduce the risk of transitioning from very mild to mild disability, further reinforcing the importance of timely intervention in the management of MS progression.

4.3.2 Impact of Environmental Exposures on MS Progression

The following section addresses what is arguably the most compelling aspect of this research: the impact of air pollution and weather conditions on MS progression over both short- and long-term periods. Among the alternative representations evaluated for each environmental variable (mean value, temporal trend, and WHO exceedance rate), the mean value consistently demonstrated the strongest performance and was therefore selected for reporting the results.

To account for feature complexity, both single- and multiple-covariate models were applied to environmental features alone as well as to environmental features combined with clinical data. However, we report

4.3. MS Progression Modeling with CTMM

only the multivariate models based on environmental features, as they yielded the best performance in this study. In the multivariate analysis, a manual grid search was conducted to identify the best-performing combinations of covariates; the results are summarized in Table 4.3. For both short- and long-term exposure windows, the optimal model included SO_2 and mean temperature.

Table 4.3: Description of each 3-state model and corresponding $-2 \times \log\text{-likelihood}$ (divided by 1000)

Description of each 3-state model	Short-term	Long-term
One-Covariate Models		
Precipitation Sum	1.650	1.647
Relative Humidity	1.650	1.640
Multi-Covariate Models		
$\text{NO}_2 + \text{CO}$	1.630	1.620
$\text{PM}_{2.5} + \text{Wind Speed} + \text{Relative Humidity} + \text{Mean Temperature}$	1.634	1.621
$\text{PM}_{2.5} + \text{PM}_{10} + \text{NO}_2$	1.632	1.619
Global Radiation + O_3	1.643	1.632
$\text{SO}_2 + \text{Mean Temperature}$	1.605	1.614
Wind Speed + Sea Level Pressure	1.647	1.644

Starting with the most influential pollutants, $\text{PM}_{2.5}$ in Figure 4.6 exhibits HRs slightly above 1 for transitions from very mild to mild disability in both the short- and long-term analyses, suggesting a potential increased risk regardless of exposure duration. This pattern indicates that patients in the earliest stages of the disease may be particularly vulnerable to $\text{PM}_{2.5}$ exposure.

For PM_{10} , the effect appears more pronounced in the short term, especially during the transition from mild to moderate-to-severe disability, but diminishes in the long-term analysis. In contrast, NO_2

4.3. MS Progression Modeling with CTMM

consistently demonstrates a statistically significant association across both short- and long-term periods, with elevated HRs observed for all transitions. This finding points to a persistent relationship between NO₂ exposure and an increased risk of MS progression, irrespective of the temporal window considered.

An intriguing result emerges for CO, where lower exposure levels are associated with a higher risk of disease progression, particularly in later stages. Although this finding may appear counterintuitive, it is consistent with evidence from a 2012 review [189] that explored the potential therapeutic role of CO in MS and related conditions. That study highlighted that, despite its classification as a toxic gas, CO is endogenously produced in small amounts and may exert anti-inflammatory effects, promote vasodilation, and modulate immune responses.

Other environmental factors, including O₃, SO₂, wind speed, and global radiation, also exhibit noteworthy patterns. In particular, O₃ shows a stronger short-term impact, especially during the transition from mild to moderate-to-severe disability, with HRs approaching 2.0.

4.3. MS Progression Modeling with CTMM

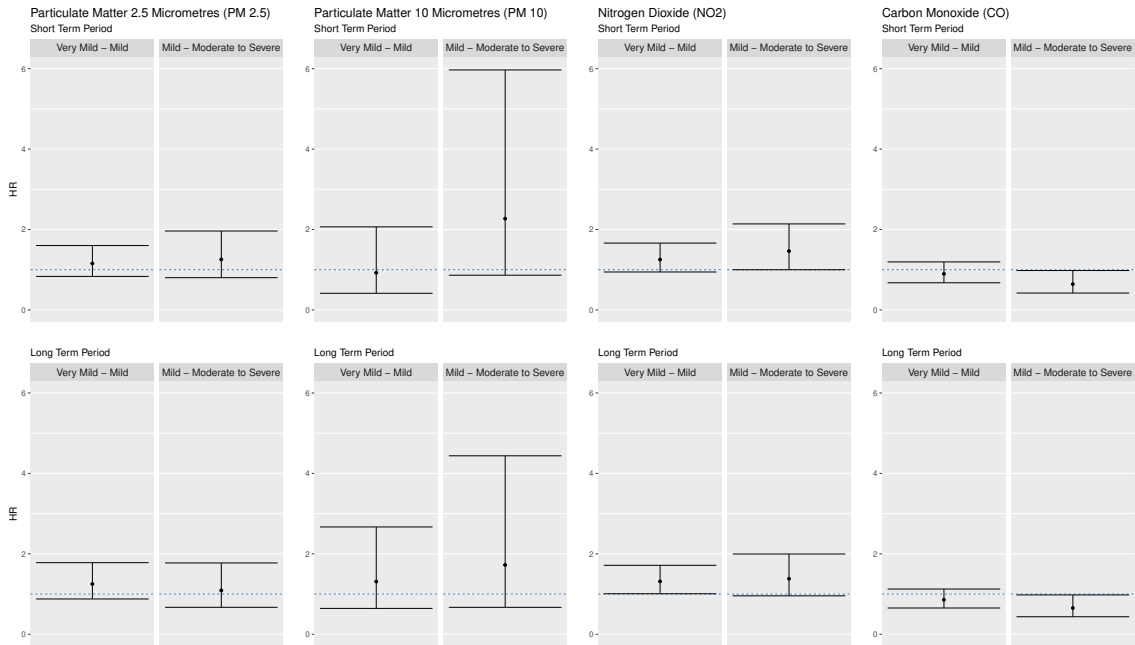


Figure 4.6: Estimated hazard ratios of some AP features on EDSS state progression transition (error bars show 95% confidence intervals)

4.3. MS Progression Modeling with CTMM

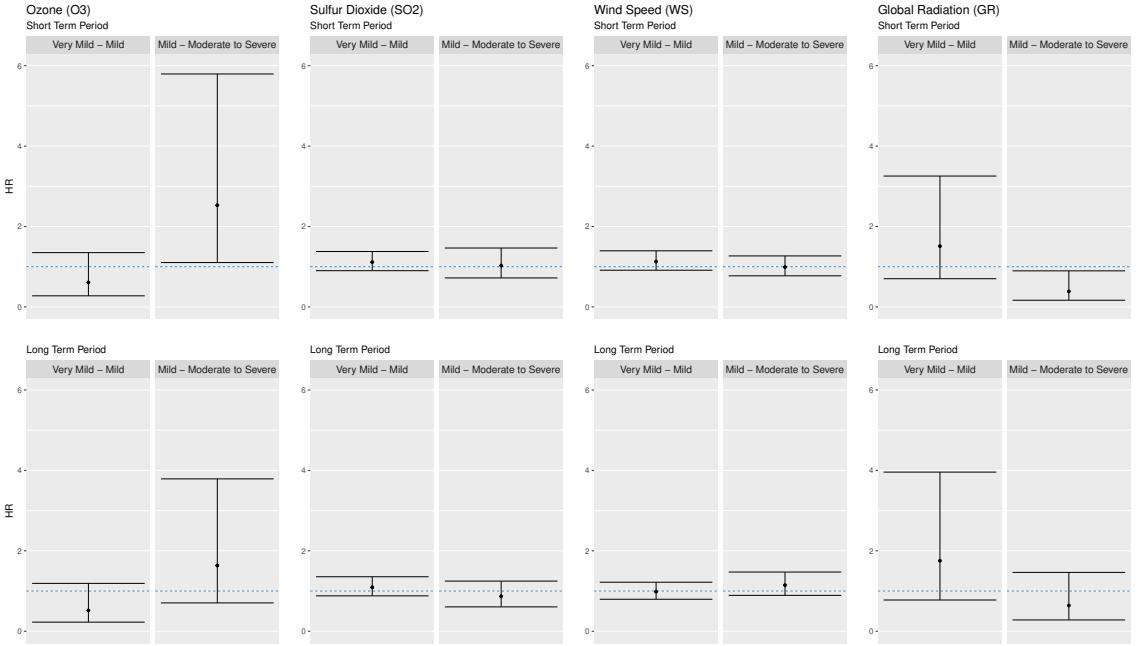


Figure 4.7: Estimated hazard ratios of the other left AP and two weather condition features on EDSS state progression transition (error bars show 95% confidence intervals)

However, this effect appears to diminish over the long term. By contrast, SO_2 does not exhibit a statistically significant association in either exposure window. Wind speed is associated with a modestly elevated short-term risk during later transitions, which becomes more pronounced in the long-term analysis, suggesting a potential increase in progression risk of 10% or more.

For global radiation, lower short-term exposure is associated with a higher risk of progression in later disease stages, although this effect weakens over time. This pattern may reflect the protective role of sunlight through vitamin D synthesis, which has been linked to reduced

4.3. MS Progression Modeling with CTMM

MS activity [74, 83]. Precipitation sum appears to act as a protective factor, particularly under long-term exposure, where it is associated with a reduced risk of progression during transitions to more severe disease states.

Temperature exhibits a contrasting pattern across disease stages: in the early stage, long-term exposure has a stronger effect than short-term exposure, whereas in later stages, short-term exposure is associated with a higher risk of progression. A similar stage-dependent pattern is observed for relative humidity. For sea-level pressure, the findings suggest that its influence becomes more relevant in the later stages of MS. Notably, under long-term exposure, an almost statistically significant association is observed, pointing to its potential role as a contributing environmental factor.

Overall, the results highlight age, relapse frequency, cerebellar involvement, and long-term environmental exposures as the primary drivers of MS progression. In summary, Table 4.4 shows that age emerges as a strong determinant of progression risk in later disease stages. Among clinical features, cerebellar scores are consistently significant across all stages and exposure windows, while pyramidal, sensory, and bladder and bowel functions also demonstrate significant long-term effects. Brainstem and visual involvement contribute variably, with borderline effects in certain transitions. Relapse frequency is strongly associated with disability worsening, particularly over the long term. Regarding treatment, first-line therapies show evidence of long-term benefit, whereas second-line therapies appear to be significant primarily in the short term, underscoring the importance of treatment timing in disease management.

4.3. MS Progression Modeling with CTMM

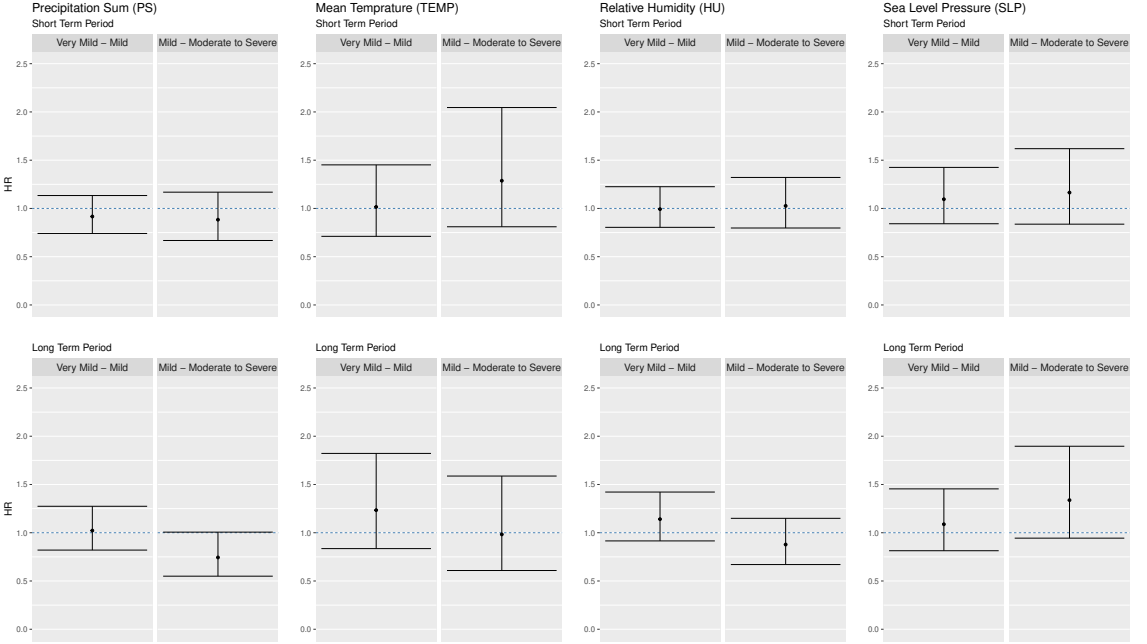


Figure 4.8: Estimated hazard ratios of the other left weather condition features on EDSS state progression transition (error bars show 95% confidence intervals)

Environmental exposures further influence MS progression. NO_2 is consistently associated with an increased risk across all transitions and exposure windows, whereas CO exhibits an unexpected protective effect that is statistically significant in the long-term analysis. Other pollutants, including O_3 and SO_2 , show borderline or stage-dependent associations, while $\text{PM}_{2.5}$ demonstrates only weak effects.

Among weather-related variables, precipitation appears to exert a protective influence in later disease stages. Global radiation and sea-level pressure display limited, stage-specific effects, whereas temperature and relative humidity do not show statistically significant associ-

4.3. MS Progression Modeling with CTMM

ations with progression.

Table 4.4: Overview of feature impact on MS progression

Feature	Very Mild to Mild		Mild to Moderate-to-Severe	
	Short-term	Long-term	Short-term	Long-term
Demographic				
Age	1.02 (0.80, 1.30)	1.02 (0.80, 1.30)	1.23 (0.92, 1.64)	1.23 (0.92, 1.64)
Sex at birth	0.98 (0.80, 1.19)	0.98 (0.80, 1.19)	0.81 (0.60, 1.10)	0.81 (0.60, 1.10)
MS in Pediatric Age	1.01 (0.84, 1.23)	1.01 (0.84, 1.23)	1.10 (0.86, 1.40)	1.10 (0.86, 1.40)
Clinical				
Pyramidal	0.95 (0.76, 1.192)	0.95 (0.76, 1.192)	1.44 (1.05, 1.97)	1.44 (1.05, 1.97)
Cerebellar	0.67 (0.48, 0.95)	0.67 (0.48, 0.95)	1.70 (1.31, 2.20)	1.70 (1.31, 2.20)
Brain Stem	0.80 (0.63, 1.03)	0.80 (0.63, 1.03)	1.17 (0.88, 1.55)	1.17 (0.88, 1.55)
Sensory	0.93 (0.70, 1.24)	0.93 (0.70, 1.24)	1.44 (1.05, 1.98)	1.44 (1.05, 1.98)
Bladder & Bowel	0.89 (0.69, 1.14)	0.89 (0.69, 1.14)	1.26 (1.06, 1.51)	1.26 (1.06, 1.51)
Visual	0.80 (0.59, 1.08)	0.80 (0.59, 1.08)	0.90 (0.61, 1.31)	0.90 (0.61, 1.31)
Mental	0.85 (0.59, 1.21)	0.85 (0.59, 1.21)	0.95 (0.65, 1.41)	0.95 (0.65, 1.41)
Other	0.89 (0.71, 1.11)	0.89 (0.71, 1.11)	0.92 (0.69, 1.22)	0.92 (0.69, 1.22)
Relapse Number	1.22 (0.92, 1.62)	1.22 (0.92, 1.62)	1.30 (1.11, 1.52)	1.30 (1.11, 1.52)
First-line Treatment	1.05 (0.94, 1.18)	0.99 (0.98, 1.01)	0.95 (0.73, 1.22)	0.97 (0.92, 1.01)
Second-line Treatment	0.68 (0.39, 0.16)	0.90 (0.79, 1.01)	1.44 (1.20, 1.73)	1.01 (0.98, 1.04)
Air Pollution				
PM _{2.5}	1.15 (0.83, 1.60)	1.24 (0.87, 1.77)	1.25 (0.80, 1.96)	1.089 (0.66, 1.77)
PM ₁₀	0.92 (0.41, 2.06)	1.30 (0.64, 2.66)	2.27 (0.86, 5.96)	1.72 (0.66, 4.43)
NO ₂	1.25 (0.94, 1.66)	1.31 (1.00, 1.71)	1.46 (0.99, 2.13)	1.38 (0.95, 1.99)
CO	0.89 (0.67, 1.19)	0.85 (0.65, 1.12)	0.64 (0.42, 0.98)	0.65 (0.43, 0.97)
O ₃	0.61 (0.27, 1.35)	0.51 (0.22, 1.19)	2.52 (1.10, 5.79)	1.63 (0.70, 3.78)
SO ₂	1.11 (0.90, 1.37)	1.09 (0.88, 1.35)	1.02 (0.72, 1.46)	0.86 (0.60, 1.24)
Weather Conditions				
Wind Speed	1.12 (0.91, 1.39)	0.98 (0.79, 1.21)	0.99 (0.77, 1.26)	1.14 (0.89, 1.47)
Global Radiation	1.51 (0.70, 3.25)	1.75 (0.77, 3.95)	0.38 (0.16, 0.89)	0.64 (0.28, 1.46)
Precipitation Sum	0.91 (0.74, 1.13)	1.02 (0.82, 1.27)	0.88 (0.66, 1.16)	0.74 (0.54, 1.00)
Mean Temperature	1.01 (0.71, 1.45)	1.23 (0.83, 1.82)	1.28 (0.81, 2.04)	0.98 (0.60, 1.58)
Relative Humidity	0.99 (0.80, 1.22)	1.14 (0.91, 1.42)	1.02 (0.79, 1.32)	0.87 (0.67, 1.14)
Sea Level Pressure	1.09 (0.84, 1.42)	1.08 (0.81, 1.45)	1.16 (0.83, 1.61)	1.33 (0.94, 1.89)

Bold values indicate statistically significant HRs.

Chapter 5

The Association of Environmental Exposure with MSSS: A Study Based on Sequential Data Modeling (Aim 3)

The objective of this chapter is to forecast the MSSS class by incorporating environmental features into a sequential data modeling framework, thereby evaluating their contribution to predictive performance. The chapter begins with a description of the preprocessing steps applied to the long-term (visit-to-visit) dataset, followed by a detailed explanation of the proposed predictive framework. Finally, the results of the modeling approach are presented and discussed. This work [190] is now available.

5.1 MSSS Sequential Dataset

The long-term dataset was employed, with each row corresponding to a distinct time window defined as the interval between consecutive clinical visits. Missing FS scores were imputed using the EWMA+LME approach, which was identified in Chapter 3 as the most effective method. To assess the robustness of the imputation strategy, we conducted a sensitivity analysis to assess whether model predictions were unduly influenced by imputed values. Specifically, we performed statistical comparisons using t-tests between predictive performances obtained from datasets with completed values and those with imputed values under varying levels of simulated Missing at Random (MAR) missingness.

The sensitivity analysis results are reported in our work [190], which indicate that, for the vast majority of the modeling settings, there were no statistically significant differences between models trained on completed versus imputed data. Statistically significant differences emerged only when missingness was artificially increased to 50%. Therefore, this does not affect the trained models, as the proportion of missing data in the training dataset is below 10%, a range within which the imputation strategy demonstrated stable and reliable behavior. These results support the robustness of the hybrid EWMA+LME approach and reduce the likelihood that the reported predictive performance is driven by imputation artifacts.

As MSSS was used as the prediction target, all records with missing MSSS values were excluded from the analysis. The remaining MSSS values were categorized into three clinically meaningful classes, based on established clinical guidelines [191] and further reviewed by clinicians to ensure an appropriate class balance. Specifically, Class 1 corresponds to values in the range [0–1) (first decile), Class 2 to [1–3) (second–third deciles), and Class 3 to values ≥ 3 (fourth–tenth deciles). These classes represent very mild (1,074 observations

5.1. MSSS Sequential Dataset

from 157 patients), mild (1,538 observations from 178 patients), and moderate-to-severe disease severity (1,410 observations from 200 patients), respectively. Table 5.1 summarizes the resulting dataset, which comprises a total of 4,022 observations from 535 patients.

To evaluate the contribution of environmental information, experiments were conducted using two versions of the dataset: (1) a baseline version containing only demographic and clinical variables (*Env-Excluded*), and (2) an extended version that incorporates the top-ranked environmental features identified through feature selection (*Env-Included*).

To further characterize disability progression, Figure 5.1 compares the distributions of EDSS and MSSS scores at patients' first and last clinical visits. At baseline, most patients exhibit lower EDSS scores (0.0–2.5) and MSSS scores (1.0–3.0), reflecting minimal to mild disability. Over time, a shift toward higher values is observed, indicating disease progression in a subset of individuals. Peaks around 1.0–1.5 for EDSS and around 1.0 for MSSS highlight the predominance of mild symptoms at baseline, whereas the increase in higher scores (≥ 6.0 for EDSS and ≥ 8.0 for MSSS) illustrates worsening disability in certain patients.

5.1. MSSS Sequential Dataset

Table 5.1: Summary of patient demographic, clinical, and environmental variables, grouped by MSSS Classes 1 to 3. Descriptive statistics are presented as count (percentage), mean (min,max), mean $\pm$ standard deviation, or median (min-max).

Feature	Total	MSSS Class 1	MSSS Class 2	MSSS Class 3
Patient	535	157	178	200
Number of Observations	1–35	1–33	1–24	1–35
MSSS	0–9.78	0.55 (0.01, 0.99)	1.87 (1.00, 2.99)	5.60 (3.04, 9.78)
Demographic				
Sex at birth (Female)	358 (67%)	107 (68.15%)	122 (68.53%)	129 (64.5%)
MS in Pediatric Age (Yes)	28 (5.3%)	8 (5.1%)	11 (6.2%)	9 (4.5%)
Age	41.8 $\pm$ 11.7	41.3 $\pm$ 10.40	38.83 $\pm$ 10.79	45.32 $\pm$ 12.64
Clinical				
Pyramidal	1 (0–6)	1 (0–3)	1 (0–5)	2 (0–6)
Cerebellar	0 (0–9)	0 (0–4)	0 (0–4)	1 (0–9)
Brainstem	0 (0–5)	0 (0–3)	0 (0–4)	1 (0–5)
Sensory	0 (0–5)	0 (0–2)	0 (0–3)	1 (0–5)
Bladder & Bowel	0 (0–2)	0 (0–6)	0 (0–6)	0 (0–5)
Visual	0 (0–9)	0 (0–4)	0 (0–5)	0 (0–9)
Mental	0 (0–4)	0 (0–1)	0 (0–2)	0 (0–4)
Other	0 (0–13)	0 (0–5)	0 (0–11)	0 (0–13)
Relapse Number	3 (0–47)	2 (0–21)	3 (0–44)	4 (0–47)
Environmental				
PM ₁₀ ($\mu\text{g}/\text{m}^3$)	32.13 $\pm$ 9.47	32.11 $\pm$ 9.24	32.27 $\pm$ 9.66	31.99 $\pm$ 9.44
PM _{2.5} ($\mu\text{g}/\text{m}^3$)	22.61 $\pm$ 8.25	22.60 $\pm$ 8.08	22.78 $\pm$ 8.47	22.43 $\pm$ 8.15
SO ₂ ($\mu\text{g}/\text{m}^3$)	4.71 $\pm$ 1.72	4.68 $\pm$ 1.72	4.65 $\pm$ 1.72	4.81 $\pm$ 1.72
O ₃ ($\mu\text{g}/\text{m}^3$)	46.11 $\pm$ 20.22	46.02 $\pm$ 18.96	45.46 $\pm$ 20.71	46.89 $\pm$ 2.58
NO ₂ ($\mu\text{g}/\text{m}^3$)	31.17 $\pm$ 10.17	31.46 $\pm$ 10.39	31.32 $\pm$ 10.22	30.78 $\pm$ 9.93
CO (mg/m ³)	0.62 $\pm$ 0.19	0.63 $\pm$ 0.20	0.62 $\pm$ 0.20	0.61 $\pm$ 0.19
Wind Speed (m/s)	2.31 $\pm$ 0.32	2.29 $\pm$ 0.30	2.33 $\pm$ 0.32	2.32 $\pm$ 0.33
Relative Humidity (%)	69.04 $\pm$ 5.10	69.08 $\pm$ 4.70	69.21 $\pm$ 5.37	68.82 $\pm$ 5.09
Global Radiation (W/m ²)	151.56 $\pm$ 56.93	152.05 $\pm$ 53.47	148.86 $\pm$ 57.56	154.12 $\pm$ 58.67
Precipitation (mm)	2.20 $\pm$ 0.95	2.22 $\pm$ 0.87	2.19 $\pm$ 0.98	2.18 $\pm$ 0.98
Mean Temperature (°C)	13.46 $\pm$ 5.56	13.47 $\pm$ 5.24	13.33 $\pm$ 5.68	13.60 $\pm$ 5.66
Min Temperature (°C)	8.84 $\pm$ 4.96	8.83 $\pm$ 4.69	8.73 $\pm$ 5.08	8.96 $\pm$ 5.02
Max Temperature (°C)	18.63 $\pm$ 6.18	18.66 $\pm$ 5.80	18.45 $\pm$ 6.31	18.81 $\pm$ 6.30
Sea Level Pressure (hPa)	1016.04 $\pm$ 3.48	1016.07 $\pm$ 3.12	1015.98 $\pm$ 3.97	1016.09 $\pm$ 3.15

Note: Class-wise patient numbers are based on the MSSS class at each patient's first observation.

5.2. Feature Selection Prior to MSSS Prediction

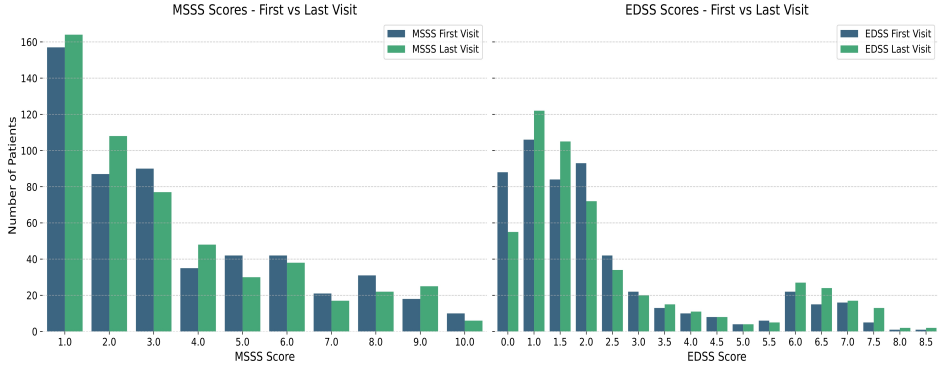


Figure 5.1: EDSS vs MSSS at first and last Visits

5.2 Feature Selection Prior to MSSS Prediction

Automatic Machine Learning (AutoML) [192, 193, 194, 195] automates key stages of ML development, including preprocessing, feature engineering, model selection, and hyperparameter tuning. By reducing manual intervention, it broadens access to ML, allowing non-experts to build competitive models. Auto-WEKA [196], Auto-sklearn [193], TPOT [195], H2O [194], and AutoGluon [197] are prominent AutoML frameworks, each employing distinct optimization strategies such as Bayesian search, genetic algorithms, and ensemble stacking. Among these, AutoGluon proposed by Amazon Web Services (AWS) AI, famous for its multilayer stacking and ability to integrate diverse models (RF [180], LightGBM [179], XGBoost [198], Fast Artificial Intelligent (FastAI) [199], k-Neighbors Distance Weighting (Weighted-KNN) [200], etc.). Balance of computational efficiency and model diversity makes it a strong choice for both academic and industrial applications [192]. It applies permutation importance [201] to quantify each feature's predic-

5.2. Feature Selection Prior to MSSS Prediction

tive contribution by measuring the drop in model accuracy after randomly shuffling its values. For instance, a score of 0.05 indicates a 5% decline in performance, suggesting that the feature carries meaningful predictive information. Shuffling disrupts the association between the feature and the target, thereby revealing its true influence [202]. A higher score indicates stronger predictive value, while negative scores suggest noisy features that may restrict performance [197] (Fig. 5.2b).

The dataset was split into training (90%) and test (10%) sets by patient ID. AutoGluon’s *TabularPredictor* performed multiclass prediction with *balanced accuracy* as the performance metric, trained for 160 seconds using the *best-quality* preset, and ranked features via permutation importance.

FS scores (see Table 5.2) emerged as the strongest predictors of MS progression, with Pyramidal ranking highest (0.1874), followed by Sensory, Cerebellar, and Other scores. This confirms the key role of clinical features—particularly pyramidal dysfunction aligned with [187]. Demographic and disease activity variables such as age and relapse count also showed high predictive value, outperforming several subscores (Brainstem, Visual, Mental, Bladder and Bowel), underscoring the importance of some basic patient characteristics [203, 204, 205].

Environmental features also showed strong predictive power, in some cases outperforming demographic factors such as gender and pediatric-onset MS. Mean $\text{PM}_{2.5}$, Mean NO_2 , and WHO Exceedance PM_{10} consistently ranked among the top predictors, whether measured as averages or temporal trends. This reinforces a robust link between air pollution and MS progression aligned with earlier evidence, including studies connecting mean PM_{10} exposure to hospital admissions in Lombardy [19] and demonstrating the influence of $\text{PM}_{2.5}$ on MS outcomes [206]. Other important environmental predictors included trends in Precipitation Sum (PS), Relative Humidity (HU), and CO, highlighting the multifactorial drivers of MS progression. Such weather-related variables may act indirectly, for example by affecting

5.3. Temporal Deep Learning Models for MSSS Class Prediction

Table 5.2: Feature importance with statistical significance. Importance scores are reported as mean with their 99% confidence interval. Values with $p < 0.05$ are considered statistically significant.

Feature	Importance Score	Std	p -value
Pyramidal	0.187 (0.143, 0.232)	0.02	< 0.001
Sensitive	0.125 (0.093, 0.157)	0.02	< 0.001
Cerebellar	0.063 (0.041, 0.085)	0.01	< 0.001
Other	0.061 (0.042, 0.080)	0.01	< 0.001
Age	0.050 (0.008, 0.091)	0.02	0.003
Relapse Number	0.045 (0.034, 0.056)	0.01	< 0.001
Brainstem	0.040 (0.020, 0.060)	0.01	< 0.001
Visual	0.018 (0.000, 0.035)	0.01	0.005
Bladder and Bowel	0.013 (0.004, 0.022)	0.00	0.001
Mental	0.005 (0.002, 0.009)	0.00	0.001
Mean PM _{2.5}	0.004 (-0.019, 0.027)	0.01	0.229
Mean NO ₂	0.003 (-0.007, 0.014)	0.01	0.115
WHO Exceedance PM ₁₀	0.003 (-0.013, 0.019)	0.01	0.216
Mean PM ₁₀	0.002 (-0.006, 0.011)	0.00	0.131
Trend of PS	0.002 (-0.001, 0.006)	0.00	0.014
Trend of HU	0.002 (-0.002, 0.005)	0.00	0.055
Trend of CO	0.001 (-0.003, 0.006)	0.00	0.125
Trend of PM _{2.5}	0.001 (-0.005, 0.006)	0.00	0.339
Trend of NO ₂	0.001 (-0.006, 0.006)	0.00	0.364

vitamin D synthesis or immune function [207].

5.3 Temporal Deep Learning Models for MSSS Class Prediction

This study focuses on RNN variants [208] for MSSS prediction. RNNs are designed to capture temporal dynamics, with outputs dependent not only on the current input but also on preceding inputs, thereby leveraging memory to retain information from past observations [209, 210]. However, training RNNs is challenging due to the

5.3. Temporal Deep Learning Models for MSSS Class Prediction

vanishing gradient problem, where gradients shrink toward zero during backpropagation, limiting the model’s ability to learn long-term dependencies because earlier time steps receive minimal weight updates. It was addressed by LSTM [211], which incorporates a memory cell (c) and three gates, forget (f), input (i), and output (o), to regulate information flow [212]. The forget gate discards irrelevant information, the input gate integrates new data, and the output gate controls what is passed forward enabling this to filter noise and preserve useful long-term dependencies across sequences. Gated Recurrent Unit (GRU) [213], a more streamlined variant of LSTM, designed with fewer parameters by eliminating the explicit memory cell. It employs only two gates: the update gate (z_t) and the reset gate (r_t). The update gate controls information flow across time, while the reset gate manages past information. This simplification reduces complexity, speeds up training, and still captures long-term dependencies.

Three architectures based on RNN, LSTM, and GRU have been developed using historical windows of varying lengths (2–4 prior observations) to predict the MSSS class from patient time-series data, as illustrated in Figure 5.2c. One-fifth of the dataset was reserved for testing, while the remainder was used for training to maintain a balanced distribution of patients across classes. To prevent overfitting, all observations from a given patient were assigned to the same subset, ensuring that no individual appeared in both training and test sets.

Additionally, to enhance robustness and generalizability, we employed five-fold cross-validation. This procedure also served to minimize validation loss. The same patient-level splitting strategy was applied within each fold during training.

Hyperparameters—including hidden size, learning rate, number of epochs, batch size, dropout rate, weight decay, and early stopping—were tuned through manual grid search to identify the values that best optimized validation performance. The final dataset comprised 342 patients in the training set, 85 in the validation set, and 108 in the test

5.3. Temporal Deep Learning Models for MSSS Class Prediction

set.



Figure 5.2: Temporal DL Framework for MSSS prediction using clinical and environmental data. The pipeline includes data preprocessing, integration of clinical, demographic, and environmental features (a), and feature selection through AutoGluon with permutation importance (b). Selected features are used to construct patient-level sequential data, which are then input into DL models to predict the MSSS class at the next clinical visit (b,c)

5.3.1 Model Input and Sequence Construction

Each patient's data were chronologically ordered by observation time, representing the sequence of visits independent of calendar dates,

5.3. Temporal Deep Learning Models for MSSS Class Prediction

enabling the model to capture temporal patterns in disease progression. Let the sequence of observations for patient p be denoted as $\mathbf{X}^p = \{\mathbf{x}_1^p, \mathbf{x}_2^p, \dots, \mathbf{x}_{T_p}^p\}$, where each $\mathbf{x}_t^p \in \mathbb{R}^d$ represents a feature vector at time step t , and T_p is the total number of observations for patient p . The corresponding outcome labels are represented as $\{y_1^p, y_2^p, \dots, y_{T_p}^p\}$. To prepare the data for model training, overlapping (or padded, if necessary) sequences of length L were constructed, generating input–output pairs for each patient as follows:

$$\mathbf{X}_j^p = [\mathbf{x}_i^p, \mathbf{x}_{i+1}^p, \dots, \mathbf{x}_{i+L-1}^p] \in \mathbb{R}^{L \times d}, \quad y_j^p = y_{i+L}^p \quad (5.1)$$

for $i = 1, \dots, T_p - L$. Each sequence $\mathbf{X}_j^p$ serves as the input, while the label y_j^p corresponds to the subsequent observation. If a patient has fewer than $L + 1$ observations, row-wise padding using the most recent available observation is applied to preserve the sequence length. Across all patients, this process produces a dataset of input–label pairs structured as a three-dimensional tensor $\mathcal{X} \in \mathbb{R}^{N \times L \times d}$, where N is the total number of sequences, L for the sequence length, and d for the dimensionality of each feature vector. The model accommodates variable-length histories, with $L \in \{2, 3, 4\}$.

5.3.2 Architectures of Deep Learning Models

Given an input sequence $X \in \mathbb{R}^{\ell \times f}$, the model processes the data through two stacked recurrent layers, using either RNN, LSTM, or GRU units. The hidden states in a generic RNN-based architecture are computed as:

$$\begin{aligned} h_t^{(1)} &= \mathcal{R}^{(1)}(x_t, h_{t-1}^{(1)}; \theta^{(1)}), \quad t = 1, \dots, \ell \\ h_t^{(2)} &= \mathcal{R}^{(2)}(h_t^{(1)}, h_{t-1}^{(2)}; \theta^{(2)}) \end{aligned} \quad (5.2)$$

Here, $x_t \in \mathbb{R}^d$ denotes the input vector at time t , and $h_t^{(1)} \in \mathbb{R}^{h_1}$, $h_t^{(2)} \in \mathbb{R}^{h_2}$ represent the hidden states of the first and second recur-

5.3. Temporal Deep Learning Models for MSSS Class Prediction

rent layers, respectively. The functions $\mathcal{R}^{(1)}$ and $\mathcal{R}^{(2)}$ are the recurrent units parameterized by $\theta^{(1)}$ and $\theta^{(2)}$. To mitigate overfitting, a dropout layer with a rate of $p = 0.1$ is applied between the recurrent layers. The resulting output is passed through a fully connected layer with ReLU activation and L2 regularization ($\lambda = 0.8$). A softmax layer then produces a probability distribution for the three output classes. Model training is carried out using categorical cross-entropy loss and optimized with the Adam optimizer, set at a learning rate of 0.001 without weight decay. Hyperparameter tuning is conducted on the training set via Grid Search, exploring hidden sizes $\{8, 16, 32, 64\}$; dropout rates $\{0.05, 0.1, 0.15, 0.2\}$; and L2 regularization values $\{0.1, 0.2, \dots, 0.8\}$. The final architecture consists of an input layer, two recurrent layers, a fully connected layer, and a softmax output layer, as summarized in Table 5.3.

Table 5.3: Model architecture and parameters

ID	Layer	Model	Hidden Size	Parameters	Output Size
1	Input	—	—	0	(2×16)
2	First Hidden Layer	RNN	16	592	(2×16)
		LSTM	16	2,368	(2×16)
		GRU	16	1,824	(2×16)
3	First Dropout	—	0.1	—	—
4	Second Hidden Layer	RNN	16	528	(2×16)
		LSTM	16	2,112	(2×16)
		GRU	16	1,632	(2×16)
5	Second Dropout	—	0.1	—	—
6	Fully Connected	—	32	544	32
7	Output	—	3	99	3

The predictive performance of RNN, LSTM, and GRU models was evaluated using four metrics: Area Under the Receiver Operating Characteristic Curve (ROC-AUC), accuracy, precision, and recall. The study aimed to (1) predict MS progression, (2) assess the added

5.3. Temporal Deep Learning Models for MSSS Class Prediction

value of environmental exposure data, (3) analyze the impact of sequence length (2, 3, or 4 prior observations) on accuracy, (4) examine model robustness as patients with longer observation histories decline over time, and (5) evaluate class-wise performance. Classes were defined by global decile groupings of the MSSS score: Class 1 (0–1, 1st decile; 1,071 observations, 239 patients), Class 2 (1–3, 2nd–3rd deciles; 1,540 observations, 312 patients), and Class 3 (>3, 4th–10th deciles; 1,411 observations, 262 patients). Disease progression was modeled using two datasets: one with only clinical and demographic variables (*Env-Excluded*) and another enriched with environmental exposures (*Env-Included*).

Figure 5.3 illustrates the performance of the three architectures trained on datasets with and without environmental features, evaluated across input sequence of 2, 3, and 4 observations. The results show that RNN-based models achieved nearly identical performance when trained solely on clinical data, without environmental inputs. The ROC-AUC scores achieved in the “four-observations” scenario are comparable, with the RNN and LSTM both scoring 0.776 and the GRU scoring 0.773. This narrow performance range indicates that the added complexity of the LSTM and GRU, including their advanced memory gating mechanisms, offers little to no advantage over the simpler RNN. This suggests that the key predictive information is either captured immediately by the basic RNN or, more likely, is absent from the clinical data stream altogether, thereby limiting the potential benefits of more complex architectures.

Incorporating environmental features consistently improved model performances across different sequence length observation scenarios, and predictive performance increased as longer input sequences were used, with four prior observations yielding the strongest results.

The best-performing configuration was the RNN model using four prior observations under the setting including Environmental data, achieving the ROC-AUC score of 0.838. Similar improvements were

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also observed in other metrics, where the RNN outperformed both LSTM and GRU under the same setting. This suggests that for this particular dataset, the simpler RNN architecture was able to exploit the combination of environmental and temporal information more effectively than the gated models. The combination yielded the largest increases in ROC-AUC and recall, indicating improved model discrimination and a greater ability to correctly identify positive instances by increasing true positives while reducing false negatives.

When comparing model architectures more broadly, LSTMs and GRUs provided more stable improvement across different metrics and sequence lengths. To quantify the association of environmental data with MS progression, we conducted a *t*-test comparing model performance across configurations (i.e., with and without environmental variables) and sequence lengths. As shown in Table 5.4, the GRU model demonstrated statistically significant improvements across metrics, particularly when using two prior observations. This improvement is most evident in the ROC-AUC, indicating that environmental variables contribute meaningful discriminative signal for distinguishing MS progression. Given the balanced class distribution, the observed gains in accuracy and recall reflect genuine improvements in predictive performance rather than misleading results caused by class imbalance. Based on these findings, we selected the GRU model for more in-depth exploration.

5.3. Temporal Deep Learning Models for MSSS Class Prediction

Table 5.4: t -test results and 95% confidence intervals comparing deep learning models with and without environmental variables. p -values less than .05 indicate statistically significant differences. The bold are the better results.

DL Model	# Obs	ROC-AUC	Accuracy	Precision	Recall
RNN	2	$p = .03$ (0.01, 0.04)	$p = .60$ (0.005, 0.056)	$p = 1$ (0.001, 0.05)	$p = .62$ (0.008, 0.052)
	3	$p = .67$ (0.02, 0.05)	$p = .25$ (0.02, 0.06)	$p = .26$ (0.02, 0.05)	$p = .87$ (0.01, 0.04)
	4	$p = .02$ (0.03, 0.07)	$p = .40$ (0.02, 0.09)	$p = .14$ (0.03, 0.09)	$p = .55$ (0.02, 0.08)
LSTM	2	$p = .24$ (0.02, 0.05)	$p = .09$ (0.04, 0.06)	$p = .11$ (0.04, 0.06)	$p = .11$ (0.03, 0.05)
	3	$p = .28$ (0.02, 0.07)	$p = .01$ (0.04, 0.08)	$p = .08$ (0.03, 0.08)	$p = .02$ (0.03, 0.07)
	4	$p = 1$ (0.02, 0.05)	$p = .40$ (0.05, 0.07)	$p = .47$ (0.04, 0.08)	$p = .79$ (0.04, 0.07)
GRU	2	$p = .03$ (0.02, 0.05)	$p = .002$ (0.04, 0.06)	$p = .06$ (0.01, 0.04)	$p = .008$ (0.03, 0.04)
	3	$p = 1$ (0.01, 0.05)	$p = .15$ (0.03, 0.05)	$p = .30$ (0.02, 0.06)	$p = 1$ (0.01, 0.04)
	4	$p = .88$ (0.01, 0.07)	$p = .14$ (0.03, 0.10)	$p = .19$ (0.03, 0.09)	$p = .32$ (0.04, 0.08)

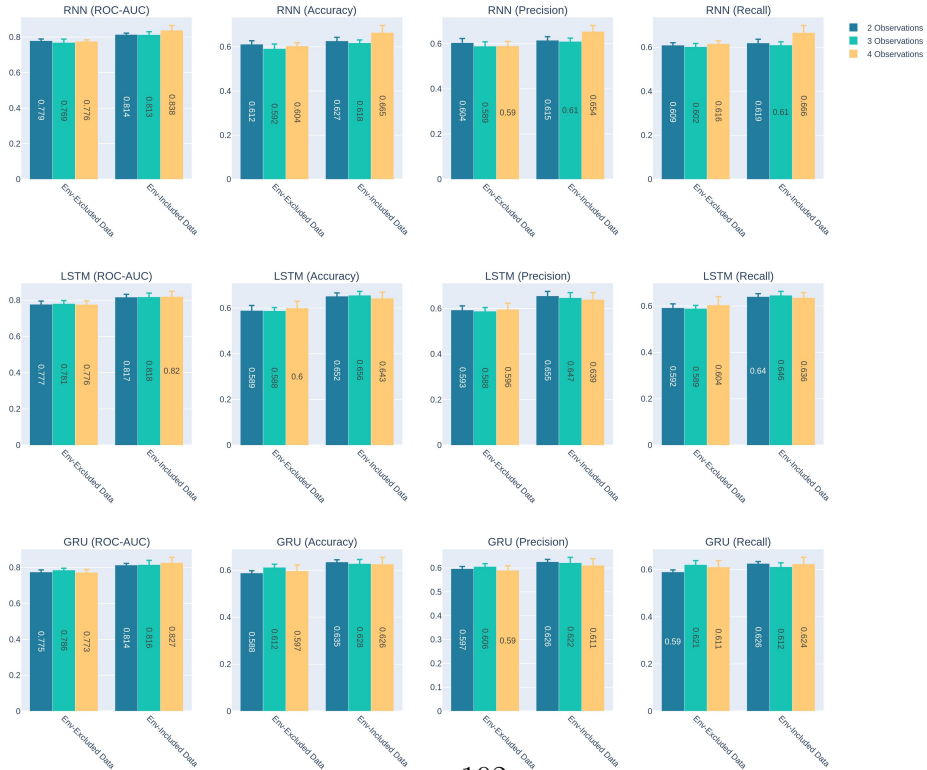


Figure 5.3: The Performance of Different DL Models with Different Sequence Lengths

5.3. Temporal Deep Learning Models for MSSS Class Prediction

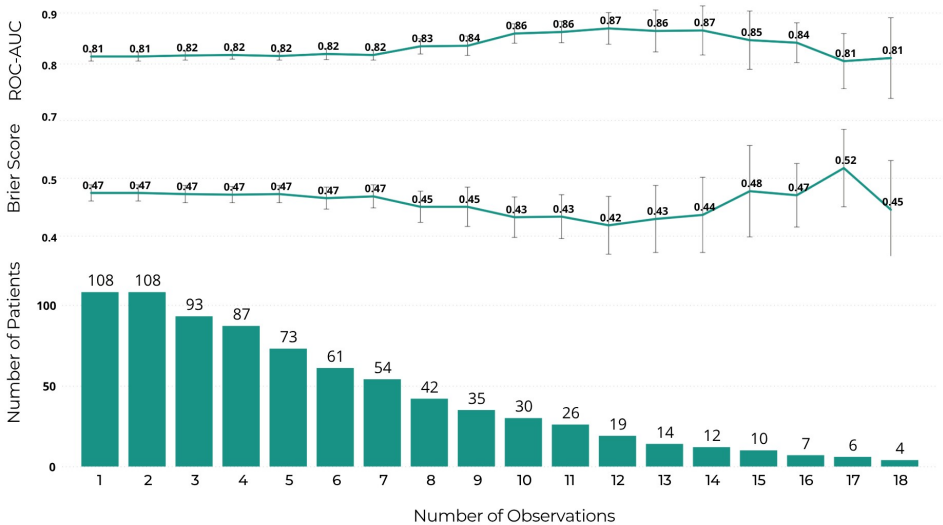


Figure 5.4: GRU model performance with two observations over time with varying patient and observation counts

Focusing on the GRU model with two observations, we analyzed how performance metrics (ROC-AUC and Brier Score) vary as the prediction window advances through patients' longitudinal data with different numbers of available observations. Figure 5.4 shows that ROC-AUC remains stable around 0.82 up to 7 observations, briefly peaks near 0.87, then declines slightly. The Brier Score follows a similar trend, stable near 0.47 up to 7 observations, dipping to 0.42, before rising above 0.52. Variability grows in both metrics at higher observation counts, reflecting smaller patient groups. Most patients have only 1 or 2 observations (108 each), with a steep drop-off in the number of patients contributing longer sequences. While longer observation windows improve predictive performance, their generalizability is limited due to the smaller, potentially biased subset of patients with extended data histories.

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To assess the choice of the proposed DL model architectures, we designed two baseline settings using RF, XGBoost, and LASSO. In the first setting, only the initial observation for each subject was used for prediction. In the second setting, baseline models were applied iteratively over time windows: predictions were generated sequentially using the first, second, and subsequent observations (up to the tenth time point) to predict the next MSSS class, and model performance was pooled as the mean across all observation-specific predictions. The DL selected model, namely a GRU using two observations, achieved a ROC AUC of 0.827, outperforming the best baseline model, LASSO using the first observation, which reached a ROC AUC of 0.76. The complete results are presented in the table below.

Table 5.5: Prediction performance of baseline models, such as RF, XGBoost, and LASSO, evaluated at baseline and across subsequent time-slice observations. At each observation time, a separate model was trained using all records available up to that time. This process was repeated for up to 10 time points to obtain time-specific performance estimates.

Observation Type	Metric	RF	XGBoost	LASSO
First Observation	ROC-AUC	0.75±0.01	0.73±0.02	0.76±0.00
	Accuracy	0.54±0.04	0.52±0.02	0.53±0.01
	Precision	0.55±0.03	0.52±0.02	0.56±0.01
	Recall	0.54±0.04	0.51±0.02	0.55±0.01
Time-Slice Observation	ROC-AUC	0.74±0.05	0.71±0.05	0.75±0.06
	Accuracy	0.53±0.07	0.56±0.07	0.54±0.07
	Precision	0.54±0.08	0.55±0.07	0.56±0.07
	Recall	0.52±0.07	0.55±0.07	0.57±0.06

Figure 5.5 illustrates the GRU model’s ROC-AUC performance with environmental features included, shown across increasing input

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sequence lengths and stratified by the three MSSS severity classes. With 2 observations, the model achieves ROC-AUC scores of 0.84 for Classes 1 and 3, and 0.76 for Class 2, indicating that the intermediate severity class remains more challenging to classify. Increasing the sequence length to 3 and 4 observations leads to marginal improvements for Classes 1 and 2, while Class 3 remains stable at 0.84. These results suggest that additional temporal context particularly benefits early-stage predictions (Class 1), whereas features of Class 3 are easily distinguishable even with fewer observations. The calibration plots indicate that the GRU models provide reasonably well-calibrated probability estimates, with Class 1 showing the lowest calibration error (Expected Calibration Error (ECE)) across all sequence lengths. Increasing the number of observations improves discrimination but leads to a modest decline in calibration, particularly for Classes 2 and 3, suggesting a tendency toward overconfident predictions as temporal context grows.

5.3.3 Model Interpretation Using SHAP Analysis

Figure 5.6 shows a post hoc SHapley Additive exPlanations (SHAP) analysis of the best-performing model, compared with pre-modeling rankings from AutoGluon. Clinical variables remain dominant, with Pyramidal, Cerebellar, and Age as top predictors. Notably, Age outranks some clinical scores (e.g., Brainstem, Sensitive, Visual), despite Sensitive being second in the AutoGluon ranking. It highlights the predictive relevance of environmental factors such as WHO Exceedance for PM_{10} , Mean $PM_{2.5}$, and NO_2 , which in some cases exceed less critical clinical variables like Mental. These results confirm the consistent importance of both clinical and selected environmental features in predicting MS progression.

In summary, a practical framework was developed for predicting the MSSS class at the subsequent visit, independent of the time interval, by integrating clinical and environmental data. Unlike prior stud-

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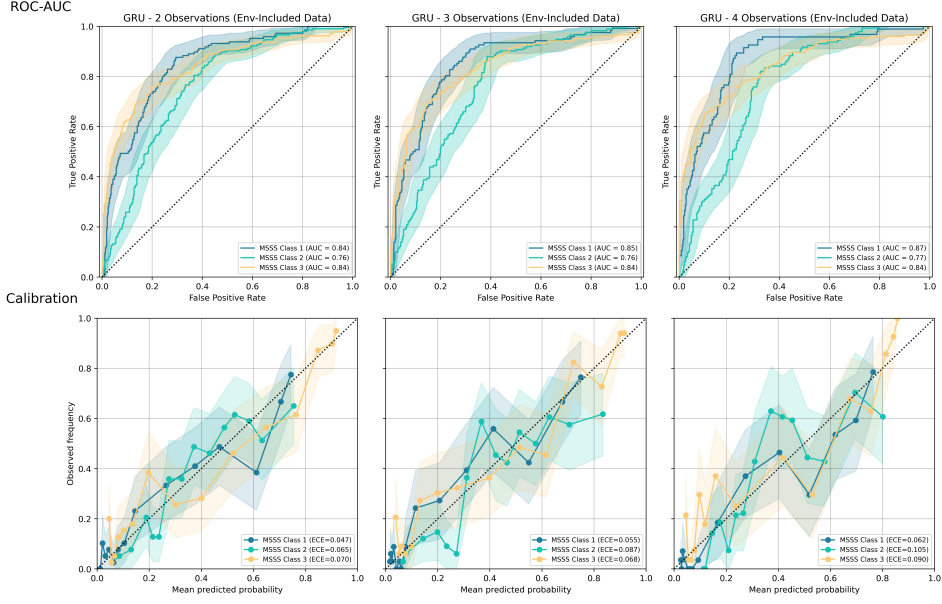


Figure 5.5: Performances of the GRU models by MSSS class. ROC-AUC and ECE values of the GRU model trained with environmental features, shown for input sequence lengths of 2, 3, and 4, and stratified by predicted MSSS class.

ies that rely primarily on imaging, this approach leverages structured tabular data derived from real-world, irregular clinical visits in combination with environmental exposures. Feature relevance was first assessed using AutoML, followed by sequential DL modeling for prediction. Results showed that incorporating environmental data significantly improved performance. Average values of PM_{10} , $PM_{2.5}$, NO_2 , PS, and HU emerged as strong predictors, in some cases surpassing demographic factors like gender or pediatric onset of MS, confirming the multifactorial nature of disease progression. Notably, even simpler models such as RNN benefited from these features. Using data from

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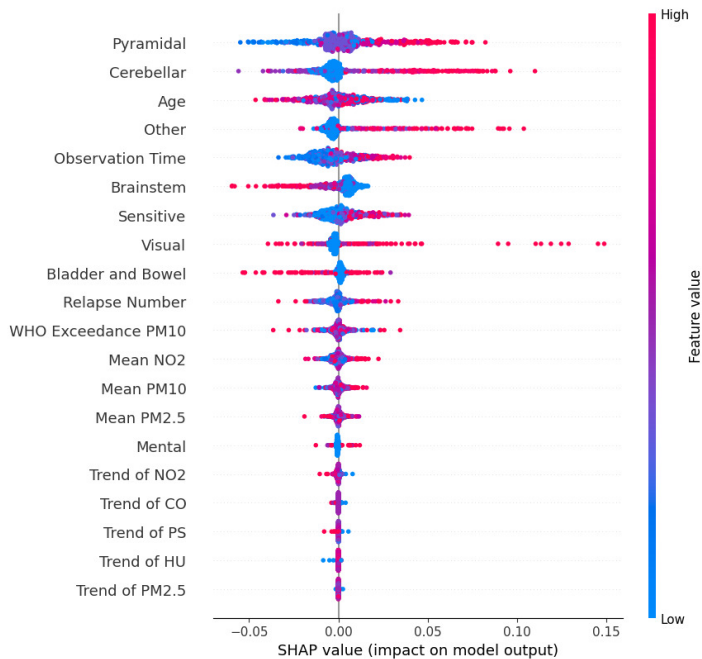


Figure 5.6: SHAP-based feature importance ranking from GRU models with two sequence lengths

only two time points already yielded strong predictions, while longer histories further enhanced performance, balancing temporal context with dataset size.

Chapter 6

Conclusions and Outlook

In order to provide effect treatments to MS patients, it is important to recognize that the environment in which they live may play a substantial role in influencing disease progression. The management of MS should not be considered solely in terms of pharmacological or medical interventions; rather, it also encompasses a range of latent factors that may be equally important. Addressing these broader determinants, such as environmental exposures, may have the potential to slow disease progression and improve quality of life. Moreover, the careful examination of patient data can yield valuable insights that assist clinicians in providing more comprehensive care. By moving beyond the traditional emphasis on inflammation and observable disability, data-driven approaches can enable healthcare professionals to develop a deeper understanding of patients' conditions during clinical consultations.

This dissertation presents an in-depth investigation of the association between MS progression and environmental exposures. A suite of AI frameworks were proposed considering air pollution and weather conditions data as a key contribution. These frameworks together

6.1. Main Achievements and Contributions

form a platform to bring environmental context into MS progression modeling, enabling both probabilistic and sequential prediction of disability states and severity scores. By integrating clinical, demographic, treatment, and environmental data, the platform provides a comprehensive foundation for understanding short- and long-term impact of exposures, and supporting prediction.

6.1 Main Achievements and Contributions

A brief review of the key challenges encountered and the novelty of the contributions is provided in this section.

6.1.1 Providing a Unified Comprehensive Longitudinal Dataset

Data is the primary tool required to initiate any analysis. However, when a lifelong disease such as MS is concerned, the key question is what data should be included to comprehensively capture its complexity. Longitudinal data can capture how the same subjects change over time, allowing models to learn dynamic patterns, trends, and temporal dependencies rather than relying on single snapshots. Repeated observations help reduce noise and account for individual baseline differences, leading to more robust and generalizable predictions. Therefore, a unified and comprehensive longitudinal dataset was constructed, integrating demographic information, clinical measures (including EDSS and FS scores), treatment history, and environmental exposures such as AP and weather conditions. These data were structured across multiple time windows, from short-term exposures (one to five weeks before each visit) to long-term exposure (six months, 1 year and visit-to-visit periods). This design enables the investigation of both immediate and cumulative impact of environmental factors on

6.1. Main Achievements and Contributions

MS progression.

6.1.2 Longitudinal Missing Data Imputation

Missing data is a major challenge not only in healthcare but also across many other domains. The effectiveness of handling missing values depends strongly on the type of data being analyzed, making the selection of appropriate strategies critical for minimizing error. This work proposes hybrid imputation approaches specifically tailored for longitudinal data—an area that has received relatively limited attention in the literature—and compares their performance against a wide range of baseline imputation methods.

6.1.3 Environmental Exposures on MS Progression

AP may have the potential to influence neurodegenerative diseases, but an important question is whether its effects differ across stages of disease progression—being more pronounced at certain stages and less so at others. Similarly, the contribution of weather conditions to MS progression remains uncertain. Using longitudinal data, the results demonstrate that CTMM provides an appropriate framework for addressing this question, as it not only identifies associations between environmental exposures and disease progression but also quantifies their stage-specific effects through the estimation of transition probabilities between disability states. This approach makes it possible to determine the stages at which specific exposures exert greater influence in either accelerating or slowing progression.

6.1.4 Association of Environmental Exposures and MSSS; A Prediction Framework

Having established the impact of environmental exposures on MS progression, the next logical step is to explore how this knowledge can be applied in predictive modeling. A central question, then, is what should be predicted. In this context, predicting MSSS, a relatively new metric for assessing disability in MS, represents a promising direction, particularly since most studies to date have relied on EDSS to measure disease severity. The findings indicate that this combination has the potential to yield significant insights, thereby contributing meaningful value to the study of disease progression in MS. This robustness indicates that reliable predictive performance can be achieved even with limited longitudinal data, which represents a key advantage in real-world clinical settings characterised by irregular patient follow-up.

6.1.5 Main Results

This section presents the principal findings of the study and explicitly relates them to the research questions outlined in Chapter 1. Specifically, the investigation addressed:

- R_1 the construction of an integrated longitudinal dataset combining clinical, demographic, treatment, and environmental data;
- R_2 the development of effective preprocessing strategies for managing missingness;
- R_3 the contribution of environmental exposures to MS progression;
- R_4 the capacity of probabilistic models such as CTMM to capture disability transitions;
- R_5 the predictive performance of sequential modelling approaches when incorporating environmental inputs;
- R_6 the short- and long-term effects of specific pollutants on different stages of MS;

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R_7 the comparative importance of environmental exposures relative to established clinical and demographic variables.

Our principal findings with respect to research issues $R1$ and $R6$ are as follows:

- Clinical data from a single MS centre were integrated with environmental measurements obtained from open-access sources, with exposure values assigned from the monitoring stations closest to each patient's postcode. Integration was performed by defining time windows preceding each clinical visit, thereby creating temporally aligned records for analysis. These exposure windows were categorised as short-term (1–5 weeks prior to the visit) or long-term (six months or the entire interval between consecutive visits). This stratification highlighted that certain associations are more pronounced over short-term exposure periods, whereas others emerge more clearly over longer-term windows. The resulting dataset forms part of the data that have recently been made publicly available in [25].

With respect to research issue R_2 , the findings indicate that:

- While simple methods can provide acceptable performance, hybrid approaches have greater potential for accurately estimating missing values in longitudinal datasets. The proposed approach achieved an error rate of 0.22, demonstrating its effectiveness in improving predictive modeling. This performance was obtained by combining temporal smoothing with subject-specific structural modeling. Furthermore, the results indicate that modeling features individually may further improve imputation accuracy.

With respect to research issues $R4$, the findings indicate that:

- CTMM, as a classical statistical approach, and AutoML, as a modern technological framework, each provide distinct insights into the role of environmental factors in MS progression. When considered together, they offer complementary perspectives that are unlikely to be fully captured by any single method, under-

6.1. Main Achievements and Contributions

scoring the continued relevance of both traditional and contemporary approaches for advancing research in this emerging field. With respect to research issues R_3 , R_6 and R_7 , the findings indicate that:

- CTMM identifies the factors that are most influential at different stages of disease progression. The results of this analysis indicate that certain environmental exposures are significantly associated with MS progression. In particular, NO_2 exposure ($\text{HR} = 1.31$) shows a significant association with disease progression during early stages, whereas O_3 exposure ($\text{HR} = 2.52$) is significantly associated with progression in later stages. In addition, AutoML analysis highlights the importance of environmental exposures in predictive modelling, with $\text{PM}_{2.5}$ and NO_2 ranking among the most influential features (p-values of 0.229 and 0.114, respectively), in some cases surpassing demographic variables such as gender or paediatric onset.

With respect to research issue R_5 , the findings indicate that:

- The effective use of data depends on aligning appropriate methods with the problems they are designed to address. In this context, integrating environmental features into sequential models proved particularly valuable for predicting the MSSS class at subsequent clinical visits. This predictive capability has clear clinical relevance, offering meaningful support to clinicians as the primary audience and intended beneficiaries of this work. The highest overall predictive performance was achieved by an RNN model trained on four longitudinal observations, yielding an ROC–AUC of 0.838 when environmental exposures were included. In contrast, the most stable and statistically significant improvement in performance between models trained with and without environmental exposures—assessed using a t-test—was observed for a GRU model trained on two observations (ROC–AUC = 0.814 with versus 0.775 without environmental expo-

tures).

6.2 Study Limitations

Several limitations of this study should be acknowledged.

First, the retrospective longitudinal design restricted the analyses to routinely collected follow-up data, which may omit relevant behavioral, socioeconomic, or biological factors influencing disease progression. Although the MSSS is a validated clinical measure, it reflects disability progression relative to disease duration and does not directly capture structural or biological changes typically assessed through imaging or molecular biomarkers.

Second, all analyses were based on data from a single clinical centre (Fondazione Mondino). This choice ensured high-quality, consistent longitudinal clinical assessments and detailed environmental exposure linkage; however, it may limit the generalisability of the findings to other clinical settings. External validation in this context presents several challenges, including the limited availability of comparable longitudinal MS cohorts, restricted access to multi-centre clinical data, and the difficulty of linking environmental and clinical information under strict anonymisation constraints. The retrospective dataset exploited in this study is the same used in the CLEF MS challenges, which was designed to support exploratory and hypothesis-generating investigations of associations and interaction patterns between environmental exposures and disease progression. While this design is well suited for methodological exploration, external validation on independent cohorts will be required and constitutes a key direction for future work. Within the BRAINTEASER project, the Mondino cohort was selected for model development due to its rich longitudinal and exposure data, while model evaluation is planned on prospective cohorts with greater geographic and socioeconomic heterogeneity, including

6.3. Future Directions

MS cohorts from Spain and Portugal.

Third, the MSSS prediction component relies on sequential deep learning models trained on a dataset comprising a few hundred patients, albeit with several tens of thousands of longitudinal observations. While such models are well suited to capturing temporal dynamics, their complexity relative to sample size may increase the risk of overfitting and limit generalisability. The availability of larger or multi-centre datasets would enable more robust model training, improved generalisation, and the exploration of alternative architectures, representing an important avenue for future research.

Finally, discretising the continuous MSSS into discrete classes necessarily reduces granularity. This classification-based formulation was adopted to enable clinically interpretable risk stratification, in line with the BRAINTEASER design and prior CLEF challenge frameworks. MSSS thresholds were defined in collaboration with clinical experts to balance interpretability and predictive feasibility. The reduced performance observed for intermediate classes may reflect overlapping disease trajectories and the absence of additional biomarkers that could further disambiguate progression patterns.

6.3 Future Directions

Four main research directions emerge as potential extensions of this work. First, incorporating additional clinical data and extending the time windows would allow a more comprehensive investigation of MS progression using the outcome proposed in this study, which is specifically tailored for MS patients. The same approach could also be applied to related neurodegenerative diseases, such as ALS.

Another promising direction involves the application of Hidden Markov Model (HMM), building on the data integration and preprocessing framework established in this work. This approach would enable in-

6.3. Future Directions

vestigation of associations between environmental exposures and not only MSSS, but also individual FS scores and relapse events. A more granular understanding of the environmental contributions to these outcomes could provide deeper insights into disease dynamics. This line of work is currently ongoing.

An important avenue for future work concerns scaling the MSSS prediction framework to larger and more diverse cohorts. Although the present study includes several tens of thousands of longitudinal observations from a few hundred patients—supporting the use of sequential DL models—expanding the number of unique individuals would increase the diversity of disease trajectories represented in the data. Larger and multi-centre datasets would enable more robust learning of heterogeneous progression patterns and facilitate improved generalisability across populations and clinical settings, while preserving the strong empirical performance observed in this work.

Another research area can be the use of ML and hybrid approaches for missing data imputation in longitudinal data. One can explore these methods to provide an interesting comparison between statistical techniques and ML-based strategies.

Last but not least, one can predict the MSSS score for the next visit, which has not been address in this research due to limited data. Treatment features may also be incorporated into the models, enabling them to capture additional aspects of disease progression.

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Abbreviations

AE	Autoencoders
AI	Artificial Intelligence
ALS	Amyotrophic Lateral Sclerosis
ANN	Artificial Neural Networks
AP	Air Pollution
AQ	Air Quality
AUC	Area Under the Curve
AutoML	Automatic Machine Learning
AWS	Amazon Web Services
BLG	Bayesian Linear Regression
BRAINTEASER	Bringing AI home for a better care of Amyotrophic Lateral Sclerosis and Multiple Sclerosis
MHC	Major Histocompatibility Complex
CART	Classification and Regression Tree
CCL27	C-C Motif Chemokine Ligand 27
CDMS	Clinically Definite Multiple Sclerosis
CHI3L1	Chitinase-3-like protein 1
CXCL13	C-X-C motif chemokine ligand 13
CHIT1	Chitinase-1

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CIS Clinically Isolated Syndrome
CLEF Conference and Labs of the Evaluation Forum
CNN Convolutional Neural Network
CNS Central Nervous System
CO Carbon Monoxide
CSF Cerebrospinal Fluid
CTMM Continuous Time Markov Model
CV Cross Validation
CVD Cardiovascular Disease
DL Deep Learning
DMT Disease Modifying Therapies
DT Decision Tree
DTMM Discrete Time Markov Model
EC European Commission
ECAD European Climate Assessment & Dataset
ECE Expected Calibration Error
EDSS Expanded Disability Status Scale
EEA European Environment Agency
EWMA Exponentially Weighted Moving Average
FastAI Fast Artificial Intelligent
FCNN Fully Connected Neural Network
FCS Standard Standard Fully Conditional Specification
FS Functional System
GB Gradient Boosting
GCN Graph-Based Convolutional Neural Network
GP Gaussian Process
GPMB Glycoprotein Non-Metastatic Melanoma Protein B
GPPM GP Progression Model
GRU Gated Recurrent Unit
HLA-DRB1 HLA class II histocompatibility antigen, DRB1 beta chain
HMM Hidden Markov Model
HR Hazard Ratio

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HU Relative Humidity
IACCTMS International Advisory Committee on Clinical Trials in Multiple Sclerosis
ICU Intensive Care Unit
IDW Inverse Distance Weighting
IL-4 Interleukin-4
JM Joint Modelling
JM MVN Joint Multivariate Normal Imputation
KNN K Nearest Neighbors
LASSO Least Absolute Shrinkage and Selection Operator
LightGBM Light Gradient Boosting Machine
LME Linear Mixed Effect
LOCF Last Observation Carried Forward
LR Linear Regression
LSTM Long Short Term Memory
MAR Missing at Random
MI Multiple Imputation
MICE Multiple Imputation with Chained Equations
ML Machine Learning
MRI Magnetic Resonance Imaging
MRS Modified Rio Score
MS Multiple Sclerosis
MSM Multi-state Model
MSSS MS Severity Score
NetCDF Network Common Data Form
Nf-L Neurofilament-light
NLP Natural Language Processing
NMSS National MS Society
NN Neural Networks
NO₂ Nitrogen Dioxide
O₃ Ozone
OCT Optical Coherence Tomography

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PCA Principal Component Analysis
PBMCs Peripheral Blood Mononuclear Cells
PIRA Progression Independent of Relapse Activity
PM Particulate Matter
PMM Predictive Mean Matching
PPMS Primary Progressive MS
PRMS Progressive Relapsing MS
PS Precipitation Sum
RF Random Forest
RIS Radiologically Isolated Syndrome
RMSE Root Mean Square Error
RNN Recurrent Neural Network
ROC-AUC Area Under the Receiver Operating Characteristic Curve
RRMS Relapsing Remitting MS
RSF Random Survival Forests
SM sclerosi multipla
SDMT Symbol Digit Modalities Test
SHAP SHapley Additive exPlanations
SLA Sclerosi Laterale Amiotrofica
SMOTE Synthetic Minority Over-sampling Technique
SO₂ Sulfur Dioxide
SPMS Secondary Progressive MS
SSE Social Support and Environment
SVM Support Vector Machine
T-cell T lymphocyte
T1 T1-weighted MRI images
T2 T2-weighted MRI images
TEMP Temperature
TS Tapping Speed
ViViT Video Vision Transformer
Weighted-KNN k-Neighbors Distance Weighting
WHO World Health Organization

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XGBoost Extreme Gradient Boosting

Publications

Journal Articles

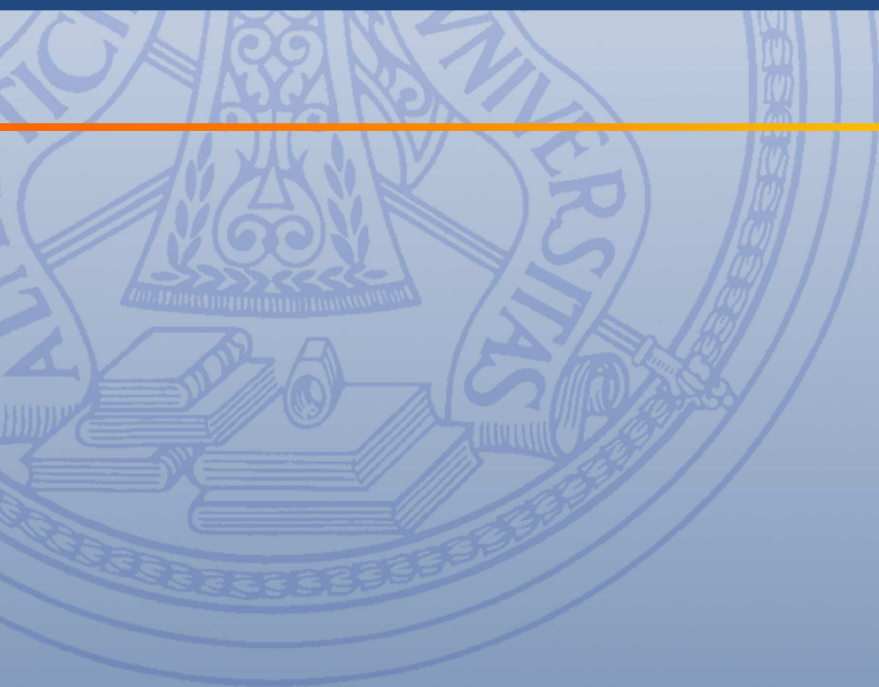
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Mahin Vazifehdan
mahin.vazifehdan01@universitadipavia.it

Università degli Studi di Pavia
via Ferrata, 5
27100 Pavia, Italy