

Investigating the Timing and Predictive Value of Clinical Conditions Preceding Multiple Sclerosis in the UK Biobank's Population-Based Cohort

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INTRODUCTION

Multiple Sclerosis (MS) is a complex autoimmune disease[1]. Growing evidence suggests a prodromal phase marked by increased healthcare use and various clinical symptoms before diagnosis, such as pain, fatigue, urinary issues, and mental health conditions[2]. These objectives are particularly relevant due to the recently highlighted increase in the age at MS onset due to a higher incidence in late-onset MS (LOMS) cases, which may result from the accumulation of different conditions[3]. However, prior studies often relied on limited time windows (5 years prior the diagnosis), introducing temporal bias by over-emphasizing conditions occurring closer to MS diagnosis, other than failing to discover associated early conditions occurring many years prior the diagnosis[4]. Moreover, the predictive value of MS prodromes and their temporal trajectories have not been explored yet.

OBJECTIVES

To investigate these aspects, we used the large UK Biobank's population-based cohort, which provided the clinical history for each individual through ICD-10 diagnosis codes and diagnoses dates. Specifically, using time-to-event analyses, we aimed to (i) identify early conditions associated with later MS diagnosis, (ii) assess their predictive value, and (iii) map disease trajectories leading to MS.

METHODS

We assessed associations between 600 clinical conditions and MS risk in 477,421 individuals using Cox models

adjusted for demographics, smoking, and MS polygenic risk score (MS-PRS). To account for multiple testing, we applied a False Discovery Rate (FDR) correction at 0.05. Statistically significant conditions were classified based on their timing of appearance in relation to MS diagnosis, i.e., >5 years, 3-5 years, 1-3 years, or within 1 year, as well as based on their clinical relationship with MS, i.e., onset symptoms, prodromal conditions, risk/protective factors, or unknown relationship. We then included these significant conditions in a LASSO Cox regression (5-fold cross-validation on 70% training-validation set) to identify key predictors, with performance assessed by the C-index and age-dependent Area Under the Curve (AUC) in the 30% test set[5]. To rank the most important conditions based on their predictive value, we used permutations. Lastly, temporal trajectories of MS-associated conditions were analyzed in MS cases using conditional logistic regression models[6].

RESULTS

We identified 192 conditions associated with MS, of which only ~20% were onset symptoms. Integrating these conditions into a predictive model already including demographics and smoking improved the C-index from 0.65 to 0.71. Among the thirty model-selected best predictors, ~25% were prodromal conditions, including neuromuscular diseases, thromboembolism, and depression which typically occurred more than five years before MS diagnosis. Including MS-PRS further increased the C-index to 0.78, with an age-dependent AUC exceeding 0.80 in individuals over 50 years. Trajectory analysis highlighted migraine as a common early diagnosis, often followed by hypertension, depression, and dorsalgia.

CONCLUSIONS

Our findings highlight early conditions and diagnostic trajectories of MS, supporting the existence of a prodromal phase. Specifically, while genetic risk represented the strongest predictor in adulthood, clinical history represented the strongest predictor in individuals over 50 years of age[7]. Importantly, the identified disease trajectories showed that MS onset symptoms occurring closer to diagnosis were themselves predictable by earlier prodromal conditions. These insights could improve MS prediction and facilitate earlier detection, particularly for late-onset cases. Future research should validate these results in independent cohorts, and explore how integrating subtle signs and symptoms, lifestyle factors and biomarkers could further refine and enhance the accuracy for an MS prediction tool to be implemented and tested in the clinical practice.

REFERENCES

1. Nylander A, Hafler DA. Multiple sclerosis. *J. Clin. Invest.* 2012;122(4):1180–1188
2. Tremlett H, Munger KL, Makhani N. The Multiple Sclerosis Prodrome: Evidence to Action. *Front. Neurol.* 2022;12
3. Prosperini L, Lucchini M, Ruggieri S, et al. Shift of multiple sclerosis onset towards older age. *J. Neurol. Neurosurg. Psychiatry* 2022;93(10)
4. Wijnands JMA, Zhu F, Kingwell E, et al. Five years before multiple sclerosis onset: Phenotyping the prodrome. *Mult. Scler. J.* 2019;25(8)
5. Bansal A, Heagerty PJ. A Tutorial on Evaluating the Time-Varying Discrimination Accuracy of Survival Models Used in Dynamic Decision Making. *Med. Decis. Mak.* 2018;38(8)
6. Han X, Hou C, Yang H, et al. Disease trajectories and mortality among individuals diagnosed with depression: a community-based cohort study in UK Biobank. *Mol. Psychiatry* 2021;26(11)
7. Misicka E, Davis MF, Kim W, et al. A higher burden of multiple sclerosis genetic risk confers an earlier onset. *Mult. Scler. J.* 2022;28(8)