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# Comparative effectiveness in multiple sclerosis: a methodological comparison

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# COMPARATIVE EFFECTIVENESS IN MULTIPLE SCLEROSIS: A METHODOLOGICAL COMPARISON

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## INTRODUCTION

In the absence of evidence from randomised controlled trials, observational data from large clinical registries can be used to emulate clinical trials and guide clinical decisions.[1] **Target trial emulation requires an explicit target-trial protocol and methodologic proficiency.** Whereas the process of randomisation ensures comparable treatment groups in clinical trials, observational studies need to carefully identify and account for potential confounders and sources of bias.[1] **Non-random treatment exposure (treatment indication bias) is inherent in clinical decision-making, as patient characteristics inform both treatment selection and clinical outcomes. Two potential techniques to reduce indication bias are propensity score (PS) matching, and marginal structural models (MSM).**

In PS matching, patients are matched at baseline on their propensity of receiving either of the compared therapies, **similar to a randomised trial.[2-4] Real-world treatment decisions do not, however, occur at a single timepoint, but are periodically reassessed. Marginal structural model (MSM), allows a continuous readjustment for potential confounders of serial treatment decisions.[2-4] The influence of time-varying covariates on the assessment of treatment response is not unique to observational data, and has also been reported to influence the interpretation of randomised clinical trials.[5]**

It remains uncertain whether simple comparisons of disease modifying therapies in cohorts with multiple sclerosis (MS) should repeatedly re-balance compared groups or a single balancing at baseline is sufficient. We have chosen a well described clinical MS scenario, the comparative effectiveness of fingolimod (FTY) and natalizumab (NAT), to **compare and contrast clinical outcomes using both PS matching and MSMs.**

## METHODS

Patients with clinically isolated syndrome or relapsing-remitting MS were identified from MSBase, a global MS registry. Included patients were treated with either NAT or FTY after 2011 **(when both treatments were available, in order to satisfy the positivity assumption),** and were not previously treated with the comparator therapy. **Baseline was the first date of treatment commencement**. Patients required assessment of disability with the Expanded Disability Status Scale (EDSS) at baseline, two subsequent timepoints >= 6 months apart, and annually thereafter. **While no minimal treatment period was specified, at least one post-baseline visit had to be recorded while treated with study therapy. Patients were censored at the time of treatment discontinuation, or at the last available visit (whichever occurred first).** To compare results from the two analytical approaches, relapses, 6-month confirmed disability accrual and improvement were studied after PS matching and with MSMs. First, propensity scores were calculated using a multivariable logistic regression model and the following covariates at baseline: MS course, age, sex, disability, MS duration, number of relapses in the prior year, number of previous MS therapies. Patients were matched, without replacement, in a 2:1 ratio using nearest-neighbour matching within 0.1 SD of the PS. Second, inverse probability of treatment weights were calculated at 6-monthly intervals using the above variables.[4] This reflected the probability of patients' treatment status at each interval given their demographic and disease history**. Covariate balance was assessed by standardised mean difference. Cumulative hazard of relapses, 6-month confirmed disability accumulation and 6-month confirmed disability improvement** were assessed with Cox proportional hazards models, and marginal structural Cox models,

respectively. **A cluster term was included per individual patient. Disability outcomes were adjusted for visit density.**

**Four hundred Monte Carlo simulations using 80% of the cohort, without replacement, were performed for each outcome to estimate the differences in mean hazard ratio (HR) and 95% confidence intervals (CI) between the two analytical approaches.**

## RESULTS

4,608 patients fulfilled the inclusion criteria (NAT 1,659, FTY 2,949). Baseline characteristics differed between groups, with higher rates of relapse (NAT:1.24 [0.96], mean [SD], vs FTY:0.89 [0.86]), higher EDSS (NAT:2.94 [1.63] vs FTY:2.36 [1.56]) and younger age (NAT:36.1 [10.3] vs FTY:38.1 [9.9]) in the natalizumab group. Covariate balance was improved by both PS matching and MSM reweighting at 6-monthly intervals, with a sustained standardised difference of <=20% for most variables (Fig 1). **Propensity score matching retained 86% of the included cohort (natalizumab 1574, fingolimod 2390). Characteristics of the PS matched and MSM cohorts were thus comparable.**

**The comparisons of outcomes were consistent between the two methods.** Treatment with natalizumab was associated with a lower probability of relapse **(PS matching: HR 0.67 [95%CI 0.60-0.76] Fig 2A.a; MSM 0.71 [0.62-0.80] Fig2B.a)** and higher probability of disability improvement **(PS matching: 1.21 [1.02-1.43] Fig 2A.c; MSM 1.43 [1.19-1.72] Fig2B.c). We did not find evidence for a difference in disability accumulation between the studied therapies with either analytical approach (PS matching: 0.96 [0.79-1.16] Fig 2A.b;**

**MSM 0.85 [0.69-**1.04] Fig2B.b). There was no statistical evidence of a difference in the magnitude of the effect size between the two methods, with point estimates of the difference in means close to null and the 95% confidence intervals including 0 (relapses [mean, 95%CI]: -0.03 [-0.17-0.11]; disability accumulation: 0.07 [-0.19-0.34]; disability regression: -0.16 [-0.43-0.10].

## DISCUSSION

**Here we have used observational data from MSBase, a large international MS registry, to emulate a head-to-head trial comparing clinical outcomes after treatment with two widely used MS therapies, FTY and NAT. The purpose of this methodological study of a well-described comparison of disease modifying therapies was to compare the efficiency of two statistical methods aimed at reducing indication bias and confounding: PS matching at baseline, and MSM with repeated re-weighting of compared groups. Results from both approaches were comparable, and consistent with the existing literature:** compared to FTY, NAT reduced the risk of relapse by 29-33%, increased the chance of disability improvement by 4-15%, and had a comparable effect on disability accumulation.[6, 7] Despite the analytical advantages of MSM to account for time-varying confounding and indication bias, the results were consistent with PS matching.

**Observational data have been used to guide clinical decision-making across the breadth of medicine.[8] In the fields of MS in particular, comparative effectiveness studies using observational data have replicated the findings from randomised controlled trials, and have frequently confirmed clinician intuition.[9, 10]**

**Since randomised controlled trials are not always feasible, the responsible and effective use of observational data is essential. The relative effectiveness of two therapies with similar structures of confounding and mediation of treatment effects can therefore be efficiently compared by either of these two methods when applied in clearly defined clinical contexts, with the use of adequately powered cohorts, and if the assumptions of causal inference are met.**

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**CONFLICT OF INTEREST**

Izanne Roos served on scientific advisory boards for Novartis and Merck and received conference travel support and/or speaker honoraria from Roche, Novartis, Biogen, Teva, Sanofi-Genzyme and Merck.

Ibrahima Diouf did not declare any competing interests.

Sifat Sharmin did not declare any competing interests.

Dana Horakova received compensation for travel, speaker honoraria and consultant fees from Biogen, Novartis, Merck Healthcare KGaA (Darmstadt, Germany), Bayer, Sanofi, Roche, and Teva, as well as support for research activities from Biogen. She was also supported by the Charles University: Cooperatio Program in neuroscience.

Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novars, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novars, and Sanofi Genzyme;received honoraria/research support from Biogen, Merck Serono, Novars, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novars, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education – project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) – funded by the European Union-Next Generation EU.

Francesco Patti received personal compensation for serving on advisory board by Almirall, Alexion, Biogen, Bristol, Berck, Novartis and Roche. I further received research grant by Biogen, Merck and Roche and by FISM, Reload Association (Onlus), Italian Health Minister, University of Catania

Vahid Shaygannejad did not declare any competing interests.

Serkan Ozakbas did not declare any competing interests.

Guillermo Izquierdo received speaking honoraria from Biogen, Novartis, Sanofi, Merck, Roche, Almirall and Teva.

Sara Eichau received speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Bayer, Sanofi Genzyme, Roche and Teva.

Marco Onofrj did not declare any competing interests.

Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Biogen, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva, and Bristol Myers Squibb. Her institutions have receved research grants from Novartis.

Raed Alroughani received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme.

Alexandre Prat did not declare any competing interests.

Marc Girard received consulting fees from Teva Canada Innovation, Biogen, Novartis and Genzyme Sanofi; lecture payments from Teva Canada Innovation, Novartis and EMD . He has also received a research grant from Canadian Institutes of Health Research.

Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.

Murat Terzi received travel grants from Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Cavit Boz received conference travel support from Biogen, Novartis, Bayer-Schering, Merck and Teva; has participated in clinical trials by Sanofi Aventis, Roche and Novartis.

Francois Grand'Maison received honoraria or research funding from Biogen, Genzyme, Novartis, Teva Neurosciences, and ATARA Pharmaceuticals.

Patrizia Sola served on scientific advisory boards for Biogen Idec and TEVA, she has received funding for travel and speaker honoraria from Biogen Idec, Merck , Teva, Sanofi Genzyme, Novartis and Bayer and research grants for her Institution from Bayer, Biogen, Merck , Novartis, Sanofi, Teva.

Diana Ferraro received travel grants and/or speaker honoraria from Merck, TEVA, Novartis, Biogen and Sanofi-Genzyme.

Pierre Grammond has served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono.

Recai Turkoglu did not declare any competing interests.

Katherine Buzzard received honoraria and consulting fees from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck, CSL and Grifols.

Olga Skibina received honoraria and consulting fees from Bayer Schering , Novartis, Merck, Biogen and Genzyme.

Bassem Yamou did not declare any competing interests.

Ayse Altintas received speaker honoraria from Merck, Alexion; received travel and registration grants from Merck.

Oliver Gerlach did not declare any competing interests.

Vincent van Pesch received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck

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Yolanda Blanco received speaker honoraira from Merck, Biogen, Brystol, Novartis and Sanofi

Davide Maimone received speaker honoraria for Advisory Board and travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva.

Jeannette Lechner-Scott,

Roberto Bergamaschi received speaker honoraria from Bayer Schering, Biogen, Genzyme, Merck , Novartis, Sanofi-Aventis, Teva; research grants from Bayer Schering, Biogen, Merck , Novartis, Sanofi-Aventis, Teva; congress and travel/accommodation expense compensations by Almirall, Bayer Schering, Biogen, Genzyme, Merck , Novartis, Sanofi-Aventis, Teva.

Rana Karabudak did not declare any competing interests.

Chris McGuigan did not declare any competing interests.

Elisabetta Cartechini did not declare any competing interests.

Michael Barnett served on scientific advisory boards for Biogen, Novartis and Genzyme and has received conference travel support from Biogen and Novartis. He serves on steering committees for trials conducted by Novartis. His institution has received research support from Biogen, Merck and Novartis.

Stella Hughes has received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche and Sanofi Genzyme.

Maria José Sa received consulting fees, speaker honoraria, and/or travel expenses for scientific meetings from Alexion, Bayer Healthcare, Biogen, Bristol Myers Squibb, Celgene, Janssen, Merck-Serono, Novartis, Roche, Sanofi and Teva.

Claudio Solaro served on scientific advisory boards for Merck, Genzyme, Almirall, and Biogen; received honoraria and travel grants from Sanofi Aventis, Novartis, Biogen, Merck, Genzyme and Teva.

Cristina Ramo-Tello received research funding, compensation for travel or speaker honoraria from Biogen, Novartis, Genzyme and Almirall.

Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering.

Daniele Spitaleri received honoraria as a consultant on scientific advisory boards by Bayer-Schering, Novartis and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva and Merck.

Aysun Soysal did not declare any competing interests.

Thor Petersen received funding from Biogen, Merck, Novartis, Sanofi-Aventis, Roche, and Genzyme

Franco Granella received an institutional research grant from Biogen and Sanofi Genzyme, served on scientific advisory boards for Biogen, Novartis, Merck, Sanofi Genzyme and Roche, received funding for travel and speaker honoraria from Biogen, Merck, and Sanofi-Aventis.

Koen de Gans did not declare any competing interests.

Pamela McCombe received speakers fees and travel grants from Novartis, Biogen, T'évalua, Sanofi

Radek Ampapa received conference travel support from Novartis, Teva, Biogen, Bayer and Merck and has participated in a clinical trials by Biogen, Novartis, Teva and Actelion.

Bart Van Wijmeersch received research and travel grants, honoraria for MS-Expert advisor and Speaker fees from Almirall, Biogen, BMS, Imcyse, Janssen, Sanofi, Merck, Novartis, Roche and Teva

Anneke van der Walt served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia.

Helmut Butzkueven received institutional (Monash University) funding from Biogen, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd and Merck; has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee.

Julie Prevost accepted travel compensation from Novartis, Biogen, Genzyme, Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva.

Jose Luis Sanchez-Menoyo accepted travel compensation from Novartis, Merck and Biogen, speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer and Teva and has participated in clinical trials by Biogen, Merck and Roche

Guy Laureys received travel and/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen.

Riadh Gouider did not declare any competing interests.

Tamara Castillo-Triviño received speaking/consulting fees and/or travel funding from Almirall, Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi-Genzyme and Teva.

Orla Gray received honoraria as consultant on scientific advisory boards for Genzyme, Biogen, Merck, Roche, and Novartis; has received travel grants from Biogen, Merck, Roche, and Novartis; has participated in clinical trials by Biogen and Merck. She has received research grant support from Biogen.

Eduardo Aguera-Morales did not declare any competing interests.

Abdullah Al-Asmi did not declare any competing interests.

Cameron Shaw received travel assistance from Biogen and Novartis.

Norma Deri received funding from Bayer, Merck , Biogen, Genzyme and Novartis.

Talal Al-Harbi did not declare any competing interests.

Yara Fragoso received honoraria as a consultant on scientific advisory boards by Novartis, Teva, Roche and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva, Roche and Merck.

Tunde Csepany received speaker honoraria/ conference travel support from Bayer Schering, Biogen, Merck , Novartis, Roche, Sanofi-Aventis and Teva.

Angel Perez Sempere did not declare any competing interests.

Irene Trevino-Frenk did not declare any competing interests.

Jan Schepel did not declare any competing interests.

Fraser Moore participated in clinical trials sponsored by EMD Serono and Novartis.

Charles Malpas did not declare any competing interests.

Tomas Kalincik served on scientific advisory boards for Roche, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD Global, Novartis, Biogen, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck.

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**FIGURE LEGENDS**

**Figure 1:** Covariate balance adjusted by propensity score matching at baseline (A) and inverse probability of treatment weighting at 6-monthly intervals in the marginal structural model (B)

**Figure 2:** Relapse and disability outcomes in natalizumab and fingolimod

As evaluated by propensity score matching (A) and marginal structural models (B):

Cumulative hazard of relapse (A.a, B.a), 6-month confirmed disability accumulation (A.b, B.b), 6-month confirmed disability improvement (A.c, B.c)

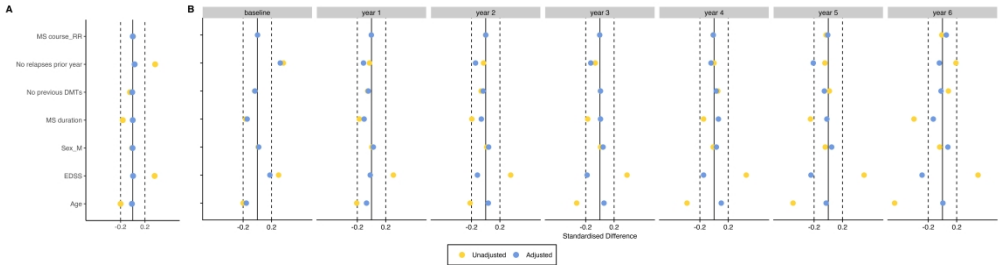



Figure 1: Covariate balance adjusted by propensity score matching at baseline (A) and inverse probability of treatment weighting at 6-monthly intervals in the marginal structural model (B)

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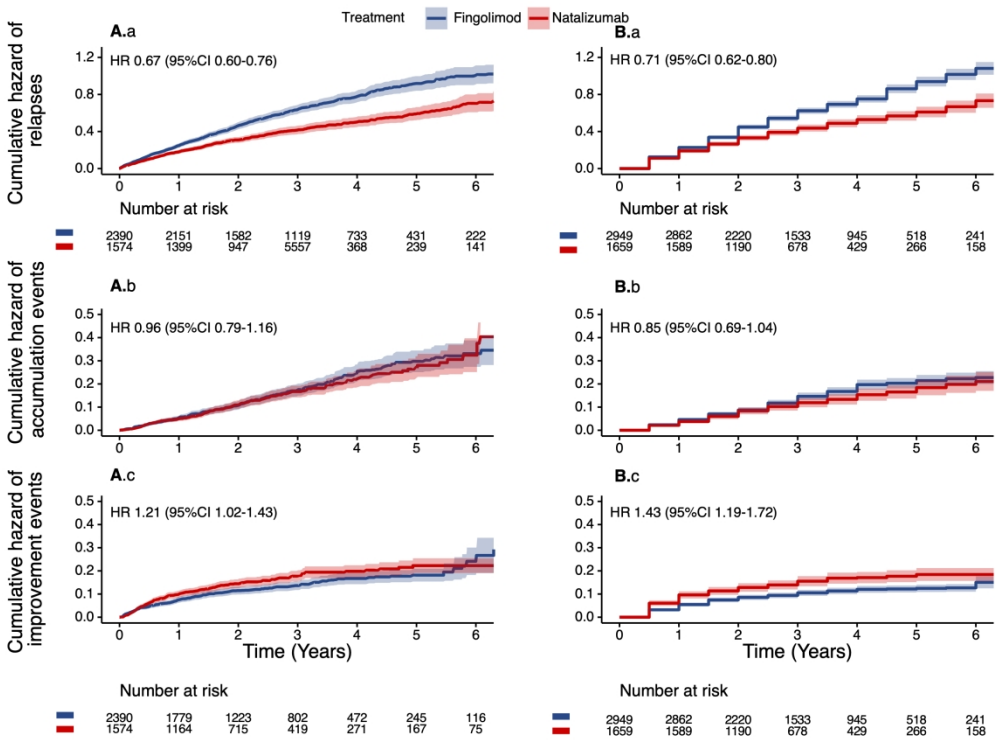



Figure 2: Relapse and disability outcomes in natalizumab and fingolimod
As evaluated by propensity score matching (A) and marginal structural models (B): Cumulative hazard of relapse (A.a, B.a), 6-month confirmed disability accumulation (A.b, B.b), 6-month confirmed disability improvement (A.c, B.c)

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