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Multiple Sclerosis: insights on COVID-19, treatments and inequalities

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Summary

This thesis presents a collection of projects on multiple sclerosis (MS), divided into three sections according to the main focus: COVID-19, treatments and inequalities. These three topics are highly interrelated: MS research during the pandemic principally focused on the impact of MS therapies, COVID-19 crisis exacerbated inequalities, disparities can be found in early access to therapies and representativeness in clinical trials. Part of the works on COVID-19 explored data from the MuSC-19 platform, where information on COVID-19 infections among patients with MS were collected. In particular, risk factors for worse course of COVID-19 were studied, in still unexplored settings or using advanced statistical methodologies, including mixture analysis and several variable selection approaches. Additionally, three surveys were conducted to explore patients' adherence to lockdown recommendations and opinions on telemedicine and to study digital work engagement of neurologists. COVID-19 pandemic speeded up the digital transformation process and findings from these surveys can surely help to direct interventions. Two articles were presented in the section on MS and treatments, with special emphasis on statistical methodology. First, a randomized clinical trial was emulated, leading to similar results compared to the original study. Second, bayesian approach was used to overcome the sample size problem in pediatric clinical trials. These studies emphasized the importance of real-word evidence in the context of rigorous target trial emulation and the utility of advanced statistical approaches to solve common issues of standard study designs. Finally, in the last section, the systematic review on race and ethnicity in MS clinical trials highlighted the need of more efforts to accurately collect and report data that adequately represent minoritized racial and ethnical groups, already at a design

phase. Moreover, statistical considerations to correctly explore the variable ‘race’ were provided, adequately unpacking the concepts of race and racism. Finally, the SocialMS study aims to provide a comprehensive overview of social determinants of health (SDOH) in the Italian MS context, with special emphasis on interrelation among SDOH, influence of SDOH on MS-related outcomes and impact of MS itself on worse SDOH. Evidence from this study can surely help to direct potential individual and structural interventions.

Preface

During my PhD program I have been actively involved in many research projects and this thesis covers a selection of studies, all in the field of Multiple Sclerosis (MS). Most of my PhD was conducted at the University of Genoa but part of the research was carried out during a 6 months visiting appointment at the University of Harvard, Department of Environmental Health.

MS is a chronic immune-mediated disease of the central nervous system and is the commonest non-traumatic disabling disease among young adults[1,2]. MS is typically diagnosed between the age of 20 and 50 and is more predominant in females[3]. Nature and severity of MS symptoms are quite heterogeneous and it can affect physical and mental functions[3].

This work is divided into three sections, according to the focus of the research projects: COVID-19, treatments and inequalities. In particular, the first section covers projects on MS and COVID-19, with special emphasis on the MuSC-19 Italian study[4]. The presented articles explored risk factors for severe COVID-19, in still unexplored settings and using advanced statistical approaches. Additionally, findings from three surveys were presented, showing patients' adherence to lockdown recommendations and telemedicine as well as neurologists' digital work engagement during the pandemic. Concerning the second section, after a brief introduction on therapies in MS, two projects presenting non-conventional statistical methodologies in the context of clinical trials were described. Finally, last section highlighted the existence of inequalities, including disparities in social determinants on health as well as racial and ethnical inequities, with special emphasis on analytical approaches to correctly study the variable 'race'. Notably,

even if the sections appear to present distinct features of MS, they are highly interrelated. For instance, research on COVID-19 and MS mainly focused on therapies, the pandemic itself caused substantial inequalities and inequities also exist in the context of treatments, in terms of both early access to disease-modifying therapies (DMTs) and representativeness in clinical research[5,6,7,8].

Multiple Sclerosis and COVID-19

Introduction

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus[9]. The first cases were observed in China in December 2019 but the virus rapidly spread worldwide and in March 2020 the World Health Organization (WHO) declared the pandemic[10,11]. Italy was the first European country to encounter the effects of COVID-19 and stringent lockdown measures were rapidly introduced[12,13]. According to lockdown measures, individuals could not leave home except for few specific reasons such as being an essential worker or other vital needs[14].

Most of the patients with MS are treated with DMTs, which affect the immune response and make patients more susceptible to infections[15,16]. Hence, COVID-19 raised additional concern in this fragile population and MS patients and their caregivers were promptly recommended to take all possible measures of prevention from COVID-19[17]. Meanwhile it was crucial to promptly and systematically collect data on COVID-19 infections in patients with MS[4].

In this emergency context, the Italian Study Group on COVID-19 infection in multiple sclerosis designed a study on MS and COVID-19 (MuSC-19) with the aim of collecting data on MS patients who got infected with COVID-19 [4,18]. As of April, 232 patients from 38 MS Italian centers were already enrolled but sample size rapidly increased over time and data collection was also expanded outside Italy[4,19,20,21,22]. Data were entered by clinicians using a web-based electronic case report form (eCRF), in accordance to the required data sharing agreements and approvals. Eligible MS patients were those who informed the neurologist about

their COVID-19 infection during an hospital/web-based visit or by phone call[16]. Infections were confirmed by a positive test for SARS-CoV-2 (reverse transcription polymerase chain reaction on nasal and pharyngeal swabs) or by a positive serological test but also data on suspected cases were collected, based on radiological findings, symptoms and contacts with confirmed cases in the 14 days before symptoms onset[16]. Data were collected retrospectively from the first contact until death or recovery from COVID-19, setting the day of first symptoms as the baseline and collecting data from patients' clinical charts[16]. Specifically, clinicians could insert in the MuSC-19 platform demographic and clinical data of patients as well as data on the course of COVID-19 infection. Demographic characteristics included age, sex, body mass index (BMI), race/ethnicity (patient-reported), employment, number of total and infected cohabitants, smoking and drinking habits (patient-reported) and comorbidities while MS history was reported as MS type (relapsing remitting - RRMS, primary progressive – PPMS, secondary progressive - SPMS), onset date, Expanded Disability Status Scale (EDSS), DMTs at baseline and date of last treatment dose[16]. Concerning COVID-19 infection, many information were collected, including possible geographical area of infection, symptoms, laboratory an radiological findings, therapies, hospitalization, pneumonia, ventilation support, intensive care unit (ICU) admission and possible recovery or death[16].

The first MuSC-19 published results appeared quite reassuring as most of the 232 patients enrolled by early April 2020 showed a mild COVID-19 course without pneumonia (96%)[4]. On the other hand, 6 patients (3%) showed a critical course (respiratory failure, septic shock, and multiple organ dysfunction or failure) and 5 of them died. Most of the patients who died were untreated except for two patients under Dimethyl fumarate and Rituximab and all had a progressive MS phenotype and EDSS of at least 6. In September, the MuSC-19 preplanned sample size of 800 patients was reached and the first findings on risk factors for severe course of

COVID-19 were published[16]. In particular, a total of 844 patients from 85 Italian MS centers were included, of whom 33% were confirmed cases. Forty-four patients (5%) died or were admitted to ICU, 92 (11%) were hospitalized or developed pneumonia. Multivariate analysis identified as risk factors for severe COVID-19 older age, male sex, methylprednisolone use the month before and anti-CD20 therapy (Ocrelizumab or Rituximab) vs no therapy. Anti-CD20 were confirmed as statistically significant risk factors for severe COVID-19 in the propensity score-weighted analysis and in all the sensitivity analyses. On the other hand, of the 73 patients under Interferon, no ICU admissions or deaths were observed. Similarly, a concomitant study including 1626 patients from the North American COVID-19 infections in MS (COViMS) registry, identified Ocrelizumab (OR=1.63) and Rituximab (OR=4.56) as risk factors for hospitalization while patients under Interferon showed a 65% odd decrease, although not statistically significant (p=0.110)[23]. Interestingly, the corresponding French study (Covisep registry) found a substantial and statistically significant reduction in the risk of severe COVID-19 among patients under Interferon or Glatiramer acetate but the analyses on DMTs were performed only at the univariate level [24]. Therefore, to further understand the impact of DMTs on COVID-19 severity, a pooled analysis including a total of 1787 patients was conducted, enrolling confirmed cases from the Italian and French cohorts, updated to the second wave[25]. This analysis shown the protective role of Interferon and confirmed anti-CD20 therapies and recent use of methyl-prednisolone as risk factors, together with older age, male sex, higher EDSS and presence of comorbidities. Additionally, the large sample size allowed to separate the effects of anti-CD20 therapies, showing a greater effect size for Rituximab (Rituximab vs other therapies: OR=3.04, p<0.001; Ocrelizumab vs other therapies: OR=1.77, p<0.001). Interestingly, other MuSC-19 studies showed that anti-CD20 therapy was also associated with reduced probability of developing antibodies after COVID-19 as well as with the number and type of symptoms [26,27]. In particular, the

serology study included 423 patients from Italy, Turkey and Brazil, of whom 77% showed a positive serological test during follow-up[26]. Patients under anti-CD20 therapies were less likely to develop antibodies compared to untreated patients (OR=0.20, p=0.002). On the other hand, the MuSC-19 study on COVID-19 signs and symptoms included a total of 1354 confirmed cases and fever, fatigue, cough and dyspnea were the most common symptoms[27]. Anti-CD20 therapy was found to be associated with a greater number of concomitant symptoms. The role of anti-CD20 was also explored in a study comparing COVID-19 outcomes in the MS Italian cohort and in the age- and sex- matched Italian general population[19]. A total of 1362 confirmed cases were included from the MuSC-19 cohort, of whom 13% were hospitalized, 2% were admitted to ICU and 2% died. Overall MS patients showed twice the risk of severe events but this excess was mainly driven by MS patients in the higher risk group (EDSS>3 and with comorbidities). Additionally, a residual substantial increase of hospitalization risk was also observed for patients under anti-CD20. Also in the Latin American MuSC-19 cohort, the use of anti-CD20 therapies was confirmed as a risk factor for hospitalization and death, despite the small sample size[21]. In particular, of the 73 patients enrolled from Brazil, Argentina, Chile, Mexico and Ecuador, 15 (21%) were hospitalized and 2 (3%) died. As expected, male sex, progressive MS, comorbidities, anti-CD20 and recent use of methylprednisolone suggested an increased risk, but only the association with anti-CD20 was statistically significant. On the other hand, in the Turkish MuSC-19 cohort no statistically significant associations were observed between DMTs and COVID-19 severity[22]. Specifically, out of 309 patients included, 81 (26%) had pneumonia, 85 (28%) were hospitalized, 9 (3%) were admitted to ICU and 3 patients died. Older age, progressive MS, high EDSS and Multiple Sclerosis Severity Score (MSSS) were identified as risk factors severe COVID-19 but in the multivariable analyses, only the role of high MSSS and progressive MS were confirmed.

Projects on MS and COVID-19

In this section, a collection of articles on MS and COVID-19 will be summarized. Most of the works were conducted using the MuSC-19 cohort data. Specifically, the first findings from the Egyptian MuSC-19 cohort were presented, two articles explored the role of air pollutants as contributors to COVID-19 severity and a multiparametric score was constructed to assess the individual risk of severe COVID-19[20,28,29, 30]. A systematic review and meta-analysis was also conducted to clarify the impact of Ocrelizumab and Rituximab on COVID-19 severity[31]. Finally, three surveys explored patients' adherence to lockdown recommendations and opinions on telemedicine as well as neurologists' digital work engagement during the pandemic[32,33,34]. To be noted that my PhD program was preceded by a research fellow position at the University of Genoa and some projects started during this period. Few articles presented in this section were published online before the start of the PhD program but were included for completeness and continuity[20,32,33,34]. The contribution to the authorship was as first[29,30], co-first[31,32,34] or second author[20,28,33].

The MuSC-19 study: The Egyptian cohort[20].

In this work the first findings from the MuSC-19 Egyptian cohort were presented. Study design was exactly the same of the Italian studies but patients were recruited from May to September 2020 from two centers in Egypt, Ain-Shams and Cairo universities. COVID-19 severity was defined as a binary variable, defining cases as severe in presence of at least one of hospitalization, ICU admission and death. Risk factors associated with COVID-19 severity were studied using univariate logistic regression models and also possible interactions between DMTs and EDSS were investigated.

A total of 119 patients were included but most were suspected COVID-19 cases (72%). Age ranged between 17 and 58 (Mean ± standard deviation: 33.90 ± 9.01 years) and most of the patients were females (77%), had a RRMS phenotype (83%). Median EDSS was 3 (Interquartile range (IQR): 2-4.5) and mean disease duration was 5.28±4.18. Interferon and Fingolimod were the most common treatments (63%) while 20 patients were under anti-CD20 (16 Rituximab and 4 Ocrelizumab). Concerning COVID-19, radiological abnormalities were observed for 60 patients (50%) and the most common symptoms were fatigue (69%), fever (66%), cough (58%), smell loss (53%), sore throat (52%) and taste loss (45%). A total of 11 patients showed a severe COVID-19 course (11 hospitalizations, 5 ICU admissions, 3 deaths). Headache was the only statistically significant risk factor for severe COVID-19 (32% vs 4%) and also patients with bone aches showed an increased risk (OR=3.84, p=0.051). On the other hand, patients who developed smell loss had reduced odd of severe COVID-19 course (OR=0.30, p=0.087).

Results were quite reassuring since only few severe cases were observed and results were in line with findings from other countries. Headache was identified as a risk factor for COVID-19 severity. However, it is a nonspecific symptom and this finding was not confirmed in larger cohorts, meaning that this could possibly be a peculiarity of the Egyptian cohort to be further validated in larger studies. The main limitation of this study was the small sample size, that probably did not allow to find statistically significant associations with well-known risk factors. Additionally, due to the small sample size we could not exclude suspected cases but it is well known that at the beginning of the pandemic, patients were not commonly tested. In conclusion, in this work we showed the first results on COVID-19 course among Egyptian MS patients, showing an acceptable safety profile and presenting some peculiar findings that need further confirmations.

The effect of air pollution on COVID-19 severity in a sample of patients with multiple sclerosis[28]

In Italy, the first cases of COVID-19 were found in January 2020 and first clusters of infections were identified in Lombardy and Veneto. The virus rapidly spread throughout the country, reaching dramatically high numbers of infections and deaths, with 4.1 million of confirmed cases and more than 120,000 deaths as of May 2021. However, the spread and severity of COVID-19 was not homogeneous across Italian regions, with the highest mortality rates observed in the northern highly polluted regions. In particular, in the Po valley, the accumulation of air pollution is influenced by geographical features, low wind speed as well as by anthropogenic emissions. Many studies have highlighted possible associations between air pollution and COVID-19 severity and air pollutants have been identified as possible risk factors for MS onset and relapses. However, the impact of air pollution on COVID-19 severity was never explored within a cohort of patients with MS and this is the objective of the study.

Data on COVID-19 course and patients' characteristics were retrieved from the MuSC-19 cohort and the patient-reported place of exposure to SARS-CoV-2 was used to assess air pollution. Specifically, we assessed long-term exposure to PM2.5 (thin particulate matter with diameter below 2.5 $\mu g/m^3$) as PM2.5 ground-level concentrations from air quality model results (Copernicus Atmospheric Monitoring Service). To retrieve long-term exposure, the 2016-2018 yearly average was calculated, since 2018 was the last year with available validated data. All the adult confirmed COVID-19 cases enrolled in the MuSC-19 by April 9 2021 with available PM2.5 data were included. In this study COVID-19 severity was defined on three levels, as mild course, hospitalization, ICU admission or death. To study the association between PM2.5 and COVID-19 severity, after checking for the assumption of proportional odds, ordered logistic regression models were

performed, also adjusting for the most relevant variables. Some sensitivity analyses were also performed. In particular, models were further adjusted for geographical area, PM2.5 concentrations were explored as tertiles and interactions of PM2.5 with BMI and presence of comorbidities were investigated.

A total of 1087 patients were included in the study, of whom 69% were females and mean age of 44.14±12.20. The most common MS phenotype was relapsing-remitting (86%) and median EDSS was 2 (IQR=1-3.5). The most common DMT was Dimethyl fumarate (18%) while 14% were under anti-CD20 and 10% under Interferon. The highest levels of PM2.5 concentrations were observed in the Po valley. Concerning COVID-19, most of the patients had a mild course while 13% were hospitalized and 2% were admitted to ICU or died. Older age, male sex, presence of comorbidities, higher EDSS and anti-CD20 therapy were identified as risk factors for severe COVID-19 while Interferon and Teriflunomide showed a protective effect. PM2.5 was identified as a risk factor for COVID-19 severity (10-unit increase: univariate analysis OR=1.44, p=0.090, multivariate analysis OR=1.90, p=0.009). Results remained consistent in all the sensitivity analyses and no statistically significant interactions were found. In particular, when PM2.5 concentrations were assessed as tertiles, all findings were confirmed (≥15.72 vs <11.57: univariate analysis OR=1.43, p=0.070, multivariate analysis OR=1.92, p=0.003).

Even if several other risk factors influence COVID-19 severity in patients with MS, high concentration of air pollutants has been identified as relevant co-factor. Chronic exposure to PM2.5 can contribute to damage of organs, making them more vulnerable to viral attack, and can also induce modifications in the immune system, facilitating pro-inflammatory and auto-aggressive responses. The main limitations of this work consist in studying only PM2.5 to assess air pollution and in the use of patient-reported place of exposure to SARS-CoV-2 to derive long-term exposure to

pollutants. Future works should surely expand and refine the definition of air pollution exposure but the relevance of this study was to show for the first time the role of pollutants as co-factors contributing to unfavorable COVID-19 within a sample of patients with MS.

The impact of PM2.5, PM10 and NO2 on Covid-19 severity in a sample of patients with multiple sclerosis: A case-control study[29]

The previous work showed the impact of air pollutants in contributing to COVID-19 severity but some limitations were illustrated and further evaluations were needed. The aim of this following study was to explore the association between air pollution and COVID-19 severity in patients with MS while accounting for more pollutants at the same time and deriving more precise information on the place of exposure. Here COVID-19 severity was defined based on the occurrence of pneumonia since it is the most common complication in severe Covid-19 patients and the presence of this condition is sufficient to differentiate COVID-19 cases between mild and moderate or severe.

This work is a case-control study which includes patients already enrolled in the MuSC-19 Italian cohort and cases were defined based on the occurrence of documented pneumonia. Suspected cases and patients who got infected after at least one dose of vaccination were excluded. As of January 28 2022, 205 patients with documented pneumonia were recorded in the MuSC-19 platform and based on sample size calculation two controls per case were required. A total of 410 controls were thus randomly selected, resulting in a of 615 patients. To retrieve accurate information on the place of exposure, all the 615 eligible patients (or caregivers) were contacted by the investigators of the MS centers and were asked “Where did you spend most of the active day (excluding sleeping hours) in the last five years?”. A new section of the MuSC-19 platform was created to allow investigators to enter the zip code of the area provided by the patients. Patients with missing zip code

were then excluded from the principal analysis but, as a sensitivity analysis, we used the zip code of the MS center as a proxy and we replicated all the analyses reinserting these patients. Air quality was assessed as 2018 annual average particulate matter (PM2.5 and PM10) and Nitrogen Dioxide (NO2) ground-level concentrations derived from air quality model results (Copernicus Atmospheric Monitoring Service). Exposure was measured in 2018 because we were interested in exposure for the last five years (2018–2022) and more recent available data were those of 2018. Characteristics of cases and controls were compared and logistic regression models were performed to explore the associations between each pollutant and COVID-19 pneumonia, also adjusting for potential confounders defined a priori (age, sex, BMI, comorbidities, EDSS, MS phenotype, MS disease duration and treatments). Correlations between pairs of pollutants were calculated using Pearson correlation coefficients. Next, exposures were explored as an environmental mixture. Specifically weighted quantile sum (WQS) logistic regression was performed to create a pollution index to explore the overall mixture effect and to identify the individual contributions of each single pollutant within the mixture, always adjusting for confounders. WQS was performed using tertiles of exposures, using the entire sample to estimate weights, generating 300 bootstrap samples and focusing on positive direction. Finally, Least Absolute Shrinkage and Selection Operator (LASSO) penalized regression model was used for variable selection, determining the penalty parameter using 10-fold cross validation and always adjusting for confounders.

Of the 615 eligible patients, 491 (169 cases and 322 controls) provided information on place of exposure and were included in the main analysis. Higher median concentrations of air pollutants were observed among cases (PM2.5: 15.86 vs 13.57, p=0.020; PM10: 19.10 vs 18.81, p=0.092; NO2: 18.69 vs 16.53, p=0.009). Additionally, cases were older, with a greater BMI, with comorbidities, more often with progressive MS phenotype, with longer disease duration, with greater EDSS

and more often under anti-CD20. We identified positive associations between air pollutants and COVID-19 pneumonia (PM2.5: 3rd vs 1st tertile: OR=2.26, 95%CI=(1.29-3.96); PM10: 3rd vs 1st tertile: OR=2.12, 95%CI=(1.22-3.68); NO2: 3rd vs 1st tertile: OR=2.12, 95%CI=(1.21-3.69)) and the main associations identified in previous studies were confirmed. Very high correlations between pairs of pollutants were observed, ranging from 0.80 to 0.97. WQS index was positively associated with COVID-19 pneumonia (β=0.44; p-value=0.004) and the most important contributors within the mixture were NO2 (41%) and PM2.5 (34%). Consistently, the set of variables selected by the LASSO was exactly the same. All the results remained consistent in the sensitivity analyses.

In this study we confirmed the association between PM2.5 and COVID-19 severity and we additionally identified NO2 and PM2.5 as the bad actors within the mixture. A substantial strength of this study consists in evaluating the complex nature of pollutants as an environmental mixture, taking into account the high correlations, deriving an overall mixture effect as well as identifying single contributors within the mixture. In particular, a positive association between exposure to the mixture and COVID-19 pneumonia was observed but PM10 was found to have a minor role in this association. The fact that PM2.5 was found to be more harmful compared to PM10 was not surprising due to the dimension of the particles. This work has some limitations. First, even if we were able to study more than one pollutants at time, future research may still increase the number of substances to be examined. Second, some people with MS are quite active and it is thus possible that they work far from their residence, or it also possible that they moved to several places in the last 5 years. In such situations, assessing a single zip code of exposure could be reductive. Third, in future research it would be interesting to additionally collect and take into consideration social determinants of health. In conclusion, air pollutants contributed to increased risk of COVID-19 pneumonia in patients with MS, individually as well as a mixture. Urgent actions

to reduce exposure to pollution should be taken, especially to protect the most vulnerable population.

A multiparametric score for assessing the individual risk of severe Covid-19 among patients with Multiple Sclerosis[30]

Several COVID-19 indexes have been developed to identify patients more at risk of hospitalization, ICU admission and death. However, these scores were not specific for patients with MS and it is known that several characteristics of the disease itself influence the prognosis of COVID-19. The aim of this study was to develop a prognostic score based on both general and MS-specific characteristics of the subjects in order to help clinicians to predict the course of COVID-19 infection.

Here COVID-19 severity was defined as mild vs hospitalization or death. The score was developed using data on confirmed COVID-19 cases enrolled in the MuSC-19 cohort from Italy, Turkey and South America between May 2020 and September 2021. Missing values for age, smoking, MS phenotype, disease duration and EDSS were imputed using multiple imputation by chained equations approach with 10 imputations, including sex, country, BMI and type of treatment as predictors. Data were then randomly separated into training (70%) and validation (30%) sets and the two datasets were compared. In the training set, univariable logistic regression models were performed, together with a multivariable model including only variables showing $p<0.10$ in the univariable analysis and excluding few variables for collinearity issues. Subsequently, variable selection was performed using three different approaches: Model 1) multivariable stepwise selection approach to select variables followed by multivariable logistic regression model with 500 bootstrap replications; Model 2) LASSO regression determining penalty parameter using 10-folds cross-validation to select variables followed by multivariable logistic regression model with 500 bootstrap replications; Model 3)

Bayesian model averaging (BMA) approach assigning equal probabilities and using 0.7 cut-off for posterior inclusion probabilities. Three scores were derived as the linear combinations of the estimated coefficients multiplied by the corresponding values of the *p* variables: $Score = \beta 1\ \text{var\_1} + \cdots + \beta p\ \text{var\_p}$.

Next, in the validation dataset, the discrimination ability of the three scores was assessed as the area under the ROC curve (AUC). Additionally, to explore the role of MS characteristics, discrimination was also assessed including only general characteristics of the patients. After having identified the best score, the optimal cut-off was identified in the training set based on the Liu criterion (maximization of the product of sensitivity and specificity) and in the validation set sensitivity, specificity were estimated. As a sensitivity analysis also other criteria were used to estimate the best cut-off (cut point on the ROC curve closest to (0,1) and Youden method). Finally, the probability of severe COVID-19 was calculated as*:*

$$Probability\ of\ severe\ COVID-19 = \frac{e^{\beta 0+\beta 1\ var\_1+\cdots+\beta p\ var\_p}}{1+e^{\beta 0+\beta 1\ var\_1+\cdots+\beta p\ \ var\_p}}$$

A total of 3852 patients were included (Italy: 47%, Turkey: 51%, South America: 2%), the mean age was 40.9±11.9 and most of the patients were female (69%). Median EDSS was 2 (IQR: 1-3), most of the patients had a relapsing remitting MS phenotype (88%) and the most common therapies were Fingolimod (16%), anti-CD20 (15%) and Dimethyl fumarate (14%). Results remained consistent after imputation of missing data. A total of 2696 patients were included in the training set, which resulted similar to the validation set for all the variables. In the training set, most of the patients showed a mild COVID-19 course (83%) and in the multivariate analysis, risk factors for severe COVID-19 were age, sex, country, comorbidities, EDSS, Methylprednisolone use and anti-CD20. When the three models for variable selection were performed, set of selected variables were largely overlapping. Except for BMI and Interferon which were only included by

the second model and Methylprednisolone use which was not included in the third model, all models selected age, sex, country, comorbidities, EDSS and anti-CD20. Inclusion of MS characteristics only slightly improved the performance of the three scores in terms of AUC and in general the three scores showed very similar performances, with the second score just slightly outperforming and being selected as the final score (AUC=0.72, 95% CI: 0.68-0.76). The selected score was thus defined as:

$$Score = 0.04\,Age + 0.42\,Male\ sex + 1.00\,Living\ in\ Turkey + 1.33\,Living\ in\ South\ America + 0.01\,BMI + 0.76\,Comorbidities + 0.11\,EDSS + 0.83\,Methylprednisolone + 0.42\,Anti\text{-}CD20 - 0.34\,Interferon$$

The observed range in the validation set was from 0.94 to 6.05, with a median of 2.90. The optimal cut-off was set to 3.02, leading to a sensitivity of 68% (95% CI: 60%-74%) and specificity of 59% (95% CI: 56%-62%). Sensitivity analyses showed consistent results. Estimated probabilities of severe COVID-19 ranged from 0.02 to 0.89 (mean: 0.17±0.13). To facilitate the use of the score in daily practice we prepared an excel spreadsheet that enables data entry of the patients' characteristics and automatically provide the derived score and the estimated probability of severe disease.

This work confirmed the role of the well-known risk factors for severe COVID-19 but its originality consists in developing a score to derive the subject-specific risk of severe COVID-19. To develop the score, many statistical methods were used and results remained quite consistent, which guarantees good reliability of variables selection. Discrimination ability of the score only slightly improved after considering MS characteristics meaning that general characteristics of the patients seem to be more relevant. Large sample size allowed to split the data into training

and validation while still maintaining large numbers but an external validation to confirm results is surely needed. Additionally, our score showed only a modest discrimination ability, a sensitivity of 0.68 and a specificity of 0.59. Due to its performance and lack of external validation, the score is not ready to be used in clinical practice to take crucial decisions such as treatments switches. However, it can still be very helpful a supplementary tool for quantifying the individual risk, in order to give the higher-risk patients an additional reason to get vaccinated against COVID-19 if they haven't done it yet and to appropriately adhere to recommendations to decrease the risk of getting infected. This score was developed including patients from Italy, Turkey and South America. To use the score in other countries, the reader can choose which is the region more similar in terms of National Health Service and management of COVID-19 cases. However, future research is surely needed to better explain differences among countries. In conclusion, we developed a score to quantify the subject-specific risk of severe COVID-19. Even if external validation and performance improvement are necessary, the score can be useful in clinical practice to provide higher-risk patients an additional reason to get vaccinated and carefully follow recommendations.

Severe outcomes of COVID-19 among patients with multiple sclerosis under anti-CD-20 therapies: a systematic review and meta-analysis[31]

This systematic review and meta-analysis was carried out to estimate COVID-19 mortality rates among patients under Rituximab and Ocrelizumab.

The systematic literature search covered material published by July 31, 2021 and was conducted in Scopus, Web of Science, PubMed, also evaluating abstracts presented at the 2020 ECTRIMS meeting. Two authors independently conducted the literature search and quality was assessed based on the Dutch Cochrane center critical review checklist proposed by MOOSE. However two domains were

removed because irrelevant in this context and thus the reporting quality score could range from 0 to 4. Only publications reporting data on COVID-19 course for patients with MS under Rituximab or Ocrelizumab were included and articles with clearly or suspicious overlapping patients were excluded. Several information were then derived, including demographic and MS characteristics as well as COVID-19 course. When some data were missing, the corresponding authors were contacted and asked for complete data. A random effects meta-analysis of proportions was performed using the continuity correction and heterogeneity was measured using the I^2 statistic. Case reports were excluded from the meta-analysis to not overestimate the rate of severe outcomes.

Of the 269 identified publications, 29 studies were finally included. Quality rate ranged from 1 to 4, with a median of 3 but after incorporating additional information provided by corresponding authors, quality rate improved, resulting in a median of 4. A total of 5173 patients were included, with samples sizes ranging from 1 to 1626; age ranged from 17 to 84 years and 71% were females. Relapsing remitting phenotype occurred in 81% of the patients, 770 (15%) and 455 (9%) were respectively treated with Ocrelizumab and Rituximab. COVID-19 was confirmed in 81% of the patients, 888 patients were hospitalized (pooled estimate: 18.1%; 95%CI = [14.5%; 21.6%], I^2=88.4%), 436 had pneumonia (pooled estimate: 14.8%; 95%CI = [9.6%; 20.1%] I^2=97.5%), 200 were admitted to ICU (pooled estimate: 3.3%; 95%CI = [1.8%; 4.7%], I^2=77.1%). A total of 115 patients died (pooled estimate: 1.8%; 95%CI = [1.0%; 2.6%], I^2=77.1%), of whom 15 under Ocrelizumab (pooled estimate: 1.6%; 95%CI = [0.6%; 2.6%]) and 10 under Rituximab (pooled estimate: 4.5%; 95%CI = [0.8%; 8.1%]).

Results were quite heterogeneous among studies, probably because data were collected from various countries, several pandemic periods and with different study designs. Pooled estimate rates of hospitalizations was 18%, slightly lower

compared to a systematic review including studies on MS and COVID-19 with no restrictions on treatments (20.7%%). Concerning pneumonia, data were often unreported, probably because of difficulties to retrieve information, especially in retrospective studies. Unexpectedly, also ICU admission data were often missing, despite their relevance in COVID-19 mortality. However, except for few samples with high percentages of ICU admissions, many studies did not observe any events. On the other hand, information on deaths were always clearly reported, also detailing treatments. Pooled estimate rate of deaths was found to be 1.8%, resulting lower compared to a previous study (3.0%). However, higher mortality rate was observed under Rituximab, consistently with previous findings in terms of hospitalizations. The greater risk in patients under Rituximab could be explained by the longer duration of the therapy compared to Ocrelizumab. In conclusion, in this systematic review and meta-analysis we estimated rates of severe COVID-19 outcomes in MS patients, with special emphasis on death under Ocrelizumab and Rituximab and we demonstrated increased risk of death for patients under Rituximab.

Adherence to social distancing and use of personal protective equipment and the risk of SARS-CoV-2 infection in a cohort of patients with multiple sclerosis[32]

This work was carried out during the first period of the pandemic when, in absence of proven effective treatments or vaccines, the Italian population was recommended to follow strict social distancing measures and progressively to adhere to lockdown. Even before the general lockdown, some recommendations were provided to fragile individuals such as patients with MS. Patients and caregivers were thus advised to stay at home and to take all possible measures of prevention from COVID-19, including the use of personal protective equipment (PPE). The aim of this study was to explore the real adherence to recommendations and its impact on the risk of COVID-19 infection within a sample of MS patients

followed in the MS center of Tor Vergata University in Rome, which is located in a low incidence area.

Data were collected through an anonymous survey, which could be completed online. A total of 916 patients received the invitation and the link to the questionnaire directly by e-mail and the questionnaire could be completed during the week 3-10 May 2020. The questionnaire was in Italian and consisted of 35-items, with questions on demographic and MS characteristics, employment, social distance measures and use of PPE, assistance for daily needs and COVID-19 infection. In case of missing data on cohabitants working habits, we assumed that half of cohabitants regularly worked outside home; when protection equipment used was not reported, it was assumed that no PPE were used; if the residency was missing, we assumed that responders lived in a low incidence province. Adherence to recommendations was assessed introducing a lockdown score (LS) on 0-10 scale, where 10 indicates full adherence. The LS was calculated as the sum of four domain scores: working (0; 4), social distancing and PPE use (0; 4), assistants for daily needs (0; 2) and residency (-2; 0), also taking into account whether cohabitants regularly went to work. Total score and specific domain scores were evaluated in relation to demographic and clinical characteristics of the patients. AUC was calculated to assess the ability of LS to discriminate patients based on having/not having come into contact with individuals positive to COVID-19 or suspected cases. The optimal LS cut-off was identified using the nearest to (0,1) method and patients were thus categorized as high/low LS. Logistic regression models were performed to study the association of LS (continuous and binary) with the risk of SARS-CoV-2 contact, also adjusting for sex, age, mobility and employment. Characteristics of the patients with low/high LS were described and logistic regression models were performed to assess the association between demographic and clinical characteristics and low LS.

A total of 551 patients completed the questionnaire. Most of the sections were completed except for the number of cohabitants who regularly worked outside home (11% missing), province of residency (0.7%) and protection equipment used (0.2%). Mean age was 44.67±11.43 years, most of the responders were females (68%), employed (65%) and lived with a partner (78%). Concerning MS, patients were mainly independent (77%) and the most common therapies were Dimethyl Fumarate (19%), Natalizumab (17%) and Fingolimod (15%). In this sample the LS mean was 6.52±2.11 (Working: 3.16±1.19, Social distancing and PPE: 2.69±1.33, Assistance 0.66±0.62) and residency penalty was applied only in 4 cases. The maximum score in the working domain was obtained by 51% of the patients but many patients were penalized due to cohabitants. Many individuals reported to work remotely, and 77 (60%) started to work in this modality due to recommendations reported in the law decree of March 8 while among those working in regular modalities, 161 had jobs considered essential. Concerning social distance and use of PPE, 81% left home for reasons different from work less than twice a week; the preferred PPE were face masks (97%) but most of the patients used surgical masks instead of FFP2/3, gloves were used by 73% of the patients. In terms of assistance, in 9% of the cases neither the patient nor the cohabitants left home to get supplies while 42% of the patients left home for personal needs, often related to MS (therapies). Domain and total LS scores were significantly higher among females and patients with mobility issues, except after taking into consideration working habits of cohabitants. LS was slightly higher among older patients but no statistical significant associations were observed; patients under immunosuppressive therapy had higher score in the assistance domain. Working individual Domain score was significantly higher among less educated individuals and unemployed, who scored better also in total LS and assistance domain. Among responders, 41 (7%) patients declared to be exposed to positive (N=10) or presumed positive (N=31) individuals and one resulted positive to COVID-19 due to contact

with a positive cohabitant. To assess LS discrimination ability, AUC was calculated and the optimal identified cut-off was derived. AUC was 0.68 (95% CI, 0.64‑0.85) and the optimal cut-off was 6, which was used to categorize patients as low (41%) or high (59%) LS. According to the multivariable logistic regression model, females had reduced risk of getting a low LS (OR=0.65, 95% CI=(0.44-0.94)), together with those needing mobility support (OR=0.37, 95% CI=(0.23-0.61)). Moreover, LS was associated with the risk of contact with COVID-19 cases, both in the continuous and binary models and after adjusting for confounders (1 unit-LS increase: OR=0.78, (95% CI=0.67; 0.90); high vs low LS: OR=0.42, (95% CI=(0.21; 0.84)). Nine of the 10 patients who came into contact with a confirmed COVID-19 case were classified as low LS; the patient who resulted positive to COVID-19 showed a LS of 5.75 (low LS).

In general, results were quite reassuring, with an overall good adherence to lockdown measures and extensive use of protection devices. We found that a 1-point increase in LS decreases the risk of COVID-19 contact of more than 20%, showing the importance of adhering to recommendations. Interestingly, females, older subjects, disabled and unemployed had higher LS, suggesting that unfavorable conditions were beneficial in this context. Even if recommendations were differentiated based on MS treatments, no relevant differences in LS were observed, meaning that it seems the MS diagnosis itself to make patients cautious. Concerning work, we observed that remote working modality was promptly introduced for many MS patients but LS working domain was often penalized due to cohabitants. If possible, according remote working also to cohabitants of fragile individuals may help to more effectively protect more vulnerable individuals. On the other hand, patients often left home to buy supplies or for reasons related to MS. More efforts are surely needed to delivery treatments at home and, if possible, to replace in persons visits with phone calls or telemedicine. This study has some limitations. First, the outcome could be inaccurate, especially when contacts with

cases were not confirmed but low numbers did not allow to define a more precise outcome. Second, data were reported by the patients through an anonymous online survey with no possibility to contact patients for clarifications and with possible imprecision. Moreover, due to the study design, possible selection bias could have occurred, but demographic and clinical characteristics of the included patients were quite similar to the general MS population. Third, this study included patients only from one MS center located in a low incidence area and we could not verify the performance of the score in other regions. In conclusion, this study demonstrated the importance of strict adherence to recommendations by MS patients and also highlighted the relevance of cohabitants behavior. Even if the validity of the score should be verified in other external samples, it represents an useful tool to measure adherence to lockdown in fragile populations.

Patient's point of view on the use of telemedicine in multiple sclerosis: a web-based survey[33]

COVID-19 pandemic had an indirect impact on patients with chronic diseases, including patients with MS. At the peak of pandemic, most of the resources were used for the management of COVID-19 and access to hospitals was limited to medical emergencies. Additionally, patients were afraid of getting infected at the hospital or through contacts with healthcare professionals. In Italy, most of the face-to-face visits were cancelled and replaced with phone or video calls, with levels of satisfactions depending on age, diagnosis, socioeconomic status, devices and presence of caregivers. This work aims to explore opinions on telemedicine within a sample of patients followed in the MS center of Tor Vergata University in Rome. Usually at the Tor Vergata MS center at least two in-persons visits were scheduled each year as routine monitoring, plus additional unscheduled visits in case of relapses or urgencies. Additionally, patients under intravenous therapies regularly went to the center for the infusions. Before pandemic, telemedicine modality was

not applied but phone calls were used in case of urgent medical needs. From March to May 2020 all the face-to-face visits were canceled according to recommendations of the Ministry of Health and replaced with phone calls. In June 2020, in person visits were allowed again but the number of visits had to be reduced. In this context, clinicians were asked to identify patients that needed in-person visits and those to be followed remotely but in the absence of guidelines, it was difficult to make decisions. This study explores opinions and preferences of the patients, in order to improve telemedicine offer, both in emergency and routine scenarios.

Data were collected using a 37-items anonymous web-based questionnaire accessible through a link sent by e-mail to 1098 patients and accessible between July 24, 2020 and September 23, 2020. Several information were collected, including demographic and MS characteristics, employment and income details, distance between home and MS center, propensity to digital health, availability and use of digital devices, digital skills, previous experience with telemedicine, remote monitoring tools, apps. Logistic univariate regression models were used to explore characteristics associated with propensity to telemedicine; multivariate models were performed including variables with $p<0.10$ in the univariate analyses separately for sociodemographic, MS, logistic and digital characteristics. Finally, a single multivariate model was fitted including all the variables with $p<0.10$ in the single-domains multivariate analyses.

A total of 613 patients were included and 54% declared to be open to telemedicine visits with the neurologist of the MS center. Responders were mainly females (70%) and 56% of the patients were 31-50 years old, most had completed at least secondary school (85%) and only 20% were unemployed. In univariate analyses, higher education, being employed or self-employed and having high income were associated with an increased propensity to telemedicine and multivariate analysis confirmed the role of education and income. Concerning MS,

most of the patients (75%) were independent and were under treatment (84%). No statistically significant associations between MS characteristics and telemedicine were found. With regard to logistic aspects, 56% of responders lived at a distance of 10-50 km from the MS center and 23% needed to be assisted by someone to reach the center. Responders more open to telemedicine were those living further from the center (>100 km vs <10km: OR=1.26, 95% CI=(1.02; 1.56)) and independently reaching the center (OR=2.13, 95% CI=(1.23; 3.66)). Almost all participants had internet at home (92%) and used e-mails (90%) and WhatsApp (82%) but only 59% used internet for remote activities and 21% and 12% used Zoom and Teams. In the univariate model, propensity to telemedicine was influenced by access to Internet, habitual use of Internet, use of computer or tablet, use of internet for remote activities, use of e-mails and use of electronic technologies to monitor workout performances but the multivariate model confirmed the impact of use of computer and tablet (OR=1.90, 95% CI=(1.06; 3.38)) and use of internet for remote activities (OR=3.09, 95% CI=(1.98; 4.85)). Results from the overall multivariate model identified higher income (p=0.037), living farther from the center (p=0.038), using computer and tablet (p=0.010) and using Internet for remote activities (p<0.001) as the statistically significant variables explaining propensity to telemedicine use. Interestingly, 57% of responders had never heard about telemedicine before COVID-19 pandemic and 70% reported saving time as the main advantage while 71% were principally worried about the impossibility to assess neurological status through telemedicine. Most of the patients (82%) preferred telemedicine compared to phone calls while 51% preferred telemedicine to in person visits but only if occasional. Of the 64 patients that had already experienced telemedicine, only 42% were independently able to connect even in presence of any technical issues but 52% were not able to connect.

COVID-19 pandemic has surely speeded up the digital transformation process of the health care system but to develop effective digital solutions it is crucial to understand patients' needs and preferences. In this study we explored thoughts on telemedicine in a large sample of MS patients. We observed that even if most of the patients were open to this new modality and most had Internet and routinely used it for several activities, some completely refused the idea of remote visits. Additionally, many of those who already experience telemedicine, were not able to connect or needed assistance. This suggests the need of providing digital education to patients in order to efficiently provide quality care. We found that highly educated patients were more open to telemedicine but surprisingly no differences in age groups were identified, probably due to the presence of only few patients with more than 70 years. Even if it is believed that one of the main advantages of telemedicine is to deliver care to disabled patients, no differences in propensity to telemedicine were observed in our sample based on MS characteristics. A possible explanation is that patients with more disability still prefer more complete in person neurological examinations. In fact, even if several tools and methods are now available, both neurologists and patients need time to get familiar and to gain trust. As expected, we found that telemedicine was preferred by people living far from the MS center. In Italy, it is actually common that patients with MS are followed in MS centers quite far from their residency due to the lack of qualified local neurological assistance. We also observed that patients with higher income were more open to telemedicine, which is in line with the fact that for most of responders the main advantage of telemedicine was saving time and not money. A limitation of this study consists in selection bias since we probably included patients with more digital skills and interest in telemedicine compared to the general MS population. In conclusion, we found that patients see telemedicine as an useful tool but to be used occasionally and still prefer face-to-face visits for an accurate evaluation of the neurological status. Telemedicine was preferred by patients living

far from the hospital, with higher income and education and with more experience and skills in the digital field. Initiatives to improve patients' digital skills would surely help to enlarge the number of patients able to adhere to this modality as well as to provide an high quality service.

Digital work engagement among Italian neurologists[34]

Social media and digital devices are increasingly used by clinicians for several purposes and digital health has profoundly changed clinical practice in the field of chronic disorders. The use of telemedicine has rapidly increased during the period of COVID-19 pandemic, when face-to-face visits were not possible. In the short period from March 1 2020 to May 21 2020, 138 telemedicine tools had been developed. In this context the role of patient has radically changed, becoming a digitally engaged patient. Digital engagement surely depends on characteristics of the patients but also the propensity to digital health of the neurologist. In 2018 the study group 'Digital Technology, Web and Social Media' of the Italian Society of Neurology (SIN) carried out an observational study to assess the digital work engagement of Italian neurologists and results revealed heterogenous views in terms of use of social media and digital devices. This work aims to assess digital work engagement among Italian neurologists during the COVID-19 pandemic period.

A total of 2850 members of the SIN were invited to participate to an online anonymous survey between September 2020 and January 2021. We collected data on demographic characteristics as well as on the use of digital devices and social media in routine practice and on the relationship with the digitally engaged patient. We fitted univariate logistic regression models to explore factors influencing the propensity to communicate with patients using social media and a multivariate model was performed including variables with $p<0.15$ in the univariate analyses.

A total of 533 neurologists were recruited, median age was 44 (IQR: 35-55) years and 48% were males. Almost half of the neurologists worked in North Italy, 30% in the South, 18% in the Center and 8% in the Islands. Almost all the responders used the computer at work (97%), followed by smartphone (79%) while only 15% used tablet and the main purpose to use devices was to stay informed on health information (85%). Wearable devices were used only by few neurologists but some would like to have them available in their clinics, especially the fit watch (47%) and the skin patch (39%). A total of 266 neurologists (48%) communicated with patients using social media while 23% were completely against the use of social media with patients. Neurologists more prone to communicate with patients using social media were older (OR=1.03, $p<0.001$), lived in central Italy (OR=1.95, $p=0.006$) or southern Italy and islands (OR=2.65, $p<0.001$). On the other hand, only few patients were in favor of friendship with patients on social media. We found that 69% of neurologists replied to patients on social media outside clinical visits; according to 58% of responders, social media had improved their relationship with patients, while 24% reported a worsening. The main social network used for working purposes was WhatsApp (86%), followed by Skype (35%) and LinkedIn (26%) while 10% had a personal website. Almost all the neurologists (86%) reported experience of patients who had already made a self-diagnosis based on the web and many neurologists declared to warn patients against inaccurate websites (72%) and to recommend reliable ones (60%).

This study explored digital work engagement of Italian neurologists during the COVID-19 pandemic period. Computers and smartphones were largely used by the neurologists while only few used tablets, probably because smartphones are more portable and still highly performant. On the other hand, only few neurologists had wearable devices but a portion of responders desired to use them. This reflects both the inaccessibility of wearable devices in clinical practice and the open debate on wearable technology over neurological examination for monitoring patients.

Almost half of the responders communicated with patients on social media but most were against friendship with patients and only few used Facebook for working purposes. This reflect the need of distinguishing between professional and personal life. On the other hand, WhatsApp was largely used, probably for both privacy and rapidity in communication even if potential confidentiality, consent, and data security issues may occur. Security problems may also occur when e-mail messages are sent to patients while platforms such as Microsoft Teams, Zoom and Webex are considered safer. Concerning telemedicine, a large implementation was observed during COVID-19 pandemic but more efforts are necessary to equip and educate healthcare professionals, to ensure protection and confidentiality and to regulate reimbursement. Interestingly, we found that neurologists from the North were less open to communicate using social media, probably because of some common behavior differences among Italian regions. On the other hand, the role of age resulted contradictory. A possible explanation is that older neurologists have established a deeper relationship with patients over years or that youth are more aware of risks and limitations of social media in the professional context. This work also highlighted the problem of fake news circulating online and of patients' self-diagnoses based on the Internet. This is a negative consequence of digitalization but we found that many neurologists help patients to distinguish between reliable and inaccurate sources of information in the web. This study has some limitations. First, possible selection bias may have occurred but characteristics of non-responders were not available and we could not make comparisons. Second, due to study design, we could not take into account MS characteristics of the patients. Additionally, further details on social media use are lacking (e.g. frequency, purpose, type of patients). Finally, this study presents the digital work engagement of neurologists during COVID-19 pandemic and the emergency context surely increased propensity to social media and telemedicine use. In conclusion, we explored digital work engagement among Italian neurologists, identifying their

opinions and habits toward digital. This analysis can surely help to direct future interventions in order to effectively take care of the digitally engaged patient.

Multiple Sclerosis and Treatments

Introduction

Even if no cure for MS is currently available, many disease-modifying therapies have been approved, especially for relapsing forms of MS[35]. The most ambitious goal is to achieve no evidence of disease activity (NEDA), which means no relapses, no new activity on magnetic resonance imaging (MRI) and no clinical disease progression[35]. Choosing the optimal individualized treatment regimen depends on many factors, including lifestyle, comorbidities, pregnancy and prognostic disease profile and timing from diagnosis to treatment initiation is crucial[35]. DMTs can be divided based on route of administration, distinguishing among injections, oral therapies and infusions as well as based on their efficacy (low, medium and high)[36]. Injection treatments include Glatiramer Acetate and Interferons, which are both considered low efficacy therapies[37]. On the other hand, examples of oral therapies are Teriflunomide (low-efficacy) and Dimethyl fumarate and Fingolimod, which are considered medium-efficacy treatments[36]. High efficacy therapies include Natalizumab, Alemtuzumab and Ocrelizumab, which are infusion therapies[36,37].

In general, safety and efficacy of therapies is demonstrated through clinical trials, which are research studies in which humans are prospectively assigned to one or more interventions (placebo or other control arms) to assess the effects of interventions[38]. In the context of MS, the rapid expansion of therapy options for RRMS has resulted in changes in clinical trials designs over time[39]. In the 1990s the first MS therapies were approved using a placebo control group but due to the availability of proven therapies, placebo-controlled designs have become unethical

over time[40,41]. Indeed, placebo designs were gradually replaced with active comparator trials, resulting in the need of larger sample sizes to detect significant treatment differences. Additionally, new study designs are emerging. For instance, phase II study of Siponimod for patients with relapsing-remitting MS employed an adaptive design[42]. Adaptive designs are flexible and efficient in the reduction of sample size, exposure to harmful or ineffective therapies and study duration[39]. However, a detailed planning and review of interim data is required and sensitive short-term outcomes need to be defined. On the other hand, only few and mainly small pragmatic trials have been conducted in the MS context[43]. Pragmatic trials assess treatment efficacy in a real-world setting in order to directly inform treatment decisions in practice while traditional clinical trials work under optimal situations which rarely occur in routine caret[39,44,45].

Projects on MS and treatments

In this section, two works on therapies for MS will be presented, with special emphasis on study design and advanced statistical methodologies. In the first article, a randomized controlled trial was emulated based on rigorous target trial emulation, using propensity scores to adjust for confounders[46]. In the second work, the problem of large sample size required in pediatric trials was overcome incorporating findings from adults trials using a Bayesian approach[47]. Contribution to the authorship was respectively as co-first[48] and second author[47].

Emulating randomised clinical trials in relapsing-remitting multiple sclerosis with non-randomised real-world evidence: an application using data from the MSBase Registry[48]

Randomized controlled trials (RCT) are the most rigorous study designs to explore causal relationships between interventions and outcomes while creating ideal conditions such as strict inclusion and exclusion criteria, masking, close monitoring of safety and adherence to treatment protocol. On the other hand, observational studies provide real-world evidence but the lack of randomization and masking may result in bias and data tend to be of lower quality compared to RCT. One approach to assess whether rigorous observational studies support causal conclusions is to make comparisons with known treatment effects in order to identify magnitude and direction of residual bias resulting from the non-randomized study design. In this study we aim to emulate an existing RCT (TRANSFORMS) using data from the MSBase registry dataset. The TRANSFORMS trial showed superior efficacy of oral fingolimod (FTY) compared with intramuscular interferon β-1-a (IFN β-1a) in terms of relapse rates and MRI outcomes.

To emulate the TRANSFORMS trial we complied with the rules for a target emulation trial. We extracted from the MSBase registry all the RRMS patients who

received IFN β-1a (weekly dose of 30 μg) or FTY (0.5 mg daily dose) between 2011 and 2021 and met the inclusion and exclusion criteria of the original trial (e.g. age, disease activity in the previous year, EDSS), but few exclusion criteria could not be evaluated due to lack of information. The first endpoint was the annualized relapse rate (ARR) defined as the number of relapses in the year after treatment initiation and several secondary endpoints were assessed, including presence of any relapses, EDSS change and time to confirmed disability progression as defined in the original trial. Data on most frequent adverse events were reported while MRI endpoints could not be assessed due to missing values. Follow-up began at treatment initiation and continued until treatment discontinuation or switch to other treatment or to a maximum follow-up of 12 months. Differences between emulated and original trial were assessed based on three binary agreement metrics: 1) the 'Regulatory agreement' metric to verify whether direction and statistical significance were confirmed; 2) the 'Estimate agreement' metric to verify if the treatment effect estimate was included within the 95% CI of the RCT estimate; 3) an evaluation of the standardized difference between RCT and emulation effect estimates followed by an hypothesis test. The principal analysis was conducted after a 1:1 PS nearest-neighbour matching with a caliper of 0.01 on the PS scale. PS was defined using a logistic regression model to estimate the probability of receiving FTY based on baseline characteristics (age, gender, MS duration, EDSS, previous therapy, calendar year, relapse history in the previous years). Several sensitivity analyses were conducted: 1) including MRI data to estimate PS; 2) performing overlap weighting approach; 3) using Mahalanobis distance to perform matching with replacement. Concerning the primary endpoints, ARR were derived from a negative binomial regression model and to take into account for center effects, the same model was replicated including center as a random effect. Logistic and ordinal logistic regression models were respectively performed to explore

presence/absence of relapses and number of relapses as categories (0, 1, 2, 3 or more); a linear regression model was fitted to study EDSS change.

We identified 4376 eligible patients who met inclusion and exclusion criteria, 3236 (74%) treated with FTY and 1140 (26%) under IFN. The two groups were largely different but after performing 1:1 PS matching (N=1712), characteristics were well balanced between the two groups, with standardized mean differences strongly reduced. Our matched cohort was not perfectly comparable to the original trial, including younger individuals, more females, more treatment-naive patients, subjects with lower previous relapse activity and lower EDSS. In our cohort, patients under FTY and IFN were followed respectively for a mean of 11.2 and 10.0 months. In the 1:1 matched cohort, the estimated ARR were 0.45 (95% CI=(0.39-0.51)) in the IFN group and 0.25 (95% CI=(0.21; 0.29)) in the FTY group, resulting in a rate ratio (RR) of 0.55 (95% CI=(0.45; 0.68)). This estimate was very close to the original trial (RR=0.49, 95% CI=(0.37; 0.64)) and all the three agreement criteria were fulfilled, also when center effect was taken into account. Superiority of FTY was also observed when relapses were assessed as absence/presence or as categories and also these findings were consistent with the original trial. EDSS change could be evaluated in 1356 patients due to missing data and no statistically significant differences were observed (−0.79 vs −0.75; p=0.591). Also in the original trial no statistically significant differences were observed (-0.08 vs 0.01, p=0.06). Only 33 events of confirmed disability progression were observed and no statistically significant differences were found, as in the original trial. Discontinuation due to adverse events was slightly more frequent under IFN (8.5% vs 4.2%), in contrast with the original trial (3.7% vs 5.6%). Information on possible adverse events were collected for 92% of the patients. Consistently with the trial, fatigue was equally reported in the two groups (7.4% and 7.5%), but no gastrointestinal disorders were observed and few events of headache and mood disorders were reported. Any laboratory data were available for less than 30% of

the subjects. Among patients with data on alanine aminotransferase levels (201 IFN, 293 FTY), abnormal results were more common in the FTY group (48.5% vs 34.3%). Similarly, out of the 487 patients with data on lymphocyte counts, abnormalities were reported for 38.1% of the IFN group and 53.4% of patients under FTY. The main findings were confirmed in all the sensitivities analyses. Specifically, when MRI data were included in PS definition, the estimated RR was 0.58 (95% CI=(0.45-0.75)), with the three agreement metrics satisfied. Similarly, when overlap weighting and Mahalanobis distance were applied, treatment effect estimates were respectively RR=0.55 (95% CI: 0.46-0.66) and RR=0.46 (95% CI: 0.35-0.60), with all metrics fulfilled.

The aim of this study was to rigorously replicate the existing TRANSFORMS trial, which led to the approval of FTY as the first oral treatment for MS. In the MS context, a previous study developed a web-based simulator to recreate in silico the setup of previous trials and they reproduced outcomes of the AFFIRM trial. In the simulated treatment group, the treatment effect was clearly evident but an unexpectedly higher percentage of relapse free subjects was observed. Outside MS, many studies employing target trial emulation have been conducted and in some works a set of several trials were emulated. In our work we successfully replicated direction, magnitude and statistical significance of the main endpoint of the RCT but there are some limitations. First, we could not apply all the exclusion criteria due to lack of complete information and our matched cohort was slightly different compared to the original one. Second, clinical practice is characterized by irregularity and heterogeneity of EDSS assessment, which can significantly impact analyses on disability progression. Finally, even if PS was calculated based on the main known confounders, unmeasured and unknown confounders could be present. In conclusion, even if lack of randomization cannot be eliminated, our study suggest that rigorous target trial emulation could provide informative results for comparative effectiveness research.

Reinterpreting Clinical Trials in Children With Multiple Sclerosis Using a Bayesian Approach[47]

In pediatric MS clinical trials, if the magnitude of effect is assumed to be similar to adults, the same sample size is required. However, due to rarity of MS in children, such trials would require a long time to be completed and Bayesian approaches may overcome this issues by incorporating findings from adults trials. In this study we aim to apply a Bayesian approach to findings from the TERIKIDS study, a negative trial which compared Teriflunomide and placebo in children with MS (57 placebo and 109 Teriflunomide).

To build the prior probability distribution, we derived the pooled hazard ratios (HRs) for time to first relapse combining published data from two randomized clinical trials in adults, the TEMSO (363 placebo and 359 Teriflunomide) and TOWER (389 placebo and 372 Teriflunomide). The log of HRs were assumed to be normal; the Bayes rule was used to derive posterior distribution, using 25% and 50% weights for the prior distribution to account for differences between adults and children. The estimated effects in TEMSO and TOWER were respectively HR=0.72 (95% CI=0.58-0.90) and HR=0.63 (95% CI=0.50-0.79) and the prior distribution was centered at HR=0.68 (95% CI=0.58-0.79). TERIKIDS trial showed a similar but not statistically significant effect (HR=0.66, 95% CI=0.39-1.11) while the posterior estimate of effect resulted statistically significant with both the weighting approaches (50%: HR=0.67 (95% CI=0.51-0.87), 25%: HR=0.67 (95% CI=0.44-0.99)).

The TERIKIDS trial found a 34% reduction which was not statistically significant and thus efficacy of Teriflunomide in children with MS could not be demonstrated. However, when findings from MS adult population were integrated, statistical significance was reached, showing the utility of Bayesian approaches in this context. However, also Bayesian approaches have some limitations, in terms of

subjectivity in prior definition and need of strong assumptions to translate results from one population to another. However, in this study, prior distribution was derived using previous published estimates and it was weighted to account for possible differences in the effects.

Multiple Sclerosis and inequalities

Introduction

SDOH are non-medical factors in which we are born, grow, live, work and age which are responsible for health inequities, leading to avoidable differences in health status[6]. Despite the increased relevance achieved in recent years, little efforts in studying and addressing SDOH has been done in the MS field, especially in Europe[6,49]. However, many associations have been found between SDOH and several MS-related outcomes[6]. SDOH can be distinguished into individual and structural factors. Individual factors are characteristics (e.g. sex, gender, sexual orientation, race, ethnicity, education, employment, socioeconomic status, domestic abuse) that influence health through interactions with structural or societal inequalities[6]. On the other hand, structural determinants include access to health care and food, social support and air pollution but the distinction between individual and structural SDOH is not always clear and factors are highly interrelated[6]. The situation is even more complex since the relationship between SDOH and MS can potentially be bidirectional, with MS itself influencing social determinants of health[6]. Moreover, several other individual or sociopolitical changes can largely impact SDOH, as shown by COVID-19 pandemic[6].

For many years, MS was seen as a disease predominantly affecting White people from North America or Europe but now it is clear that it is a global disease[50,51,52]. Distinctive differences in MS have been observed by race/ethnicity groups, including age of onset, environmental risk factors, disease severity, progression, mortality, therapy response and tolerability[53,54,55,6]. These observed differences are unlikely to be solely explained by genetics, while they are probably

influenced by SDOH and derive from systematic racism[6,56]. Moreover, disparities for minoritized racial and ethnical groups can be even found in lack of adequate representativeness in clinical research[57]. Other disparities can be observed by level of education. Indeed, evidence suggests the influence of education on MS clinical outcomes, including disability progression and cognitive impairment[58,59]. However, education is highly interrelated with other risk factors for MS onset and worse course, including smoking, health literacy, unemployment and low socioeconomic status and it is not easy to disentangle the contribution of each single factor[6]. Additionally, MS itself may limit educational achievements as well as employment status. Similarly, also employment status interacts with many factors and unemployment was found to be associated with several poor outcomes in MS, including disability, fatigue, cognitive impairment and physical and mental quality of life[60,61,62,63,64]. Interestingly contradictory findings were observed when the probability of leaving employment was compared by sex[61,65,66]. In general, effects of MS on quality of life have been found to vary between males and females but the social construct of gender is more complex than binary and is also interrelated to disparities in access to care[67,68,6]. Indeed, a study conducted in Italy found that lesbian, gay, bisexual and transgender (LGBT) patients had reduced access to psychological services and were more likely to change MS Center compared to heterosexuals, with changes influenced by homophobic episodes[69]. Another relevant SDOH is socioeconomic status, which is a complex construct including income, occupation and residence that results in inequities also in countries with an universal health care-system[6]. Specifically, low socioeconomic status has been associated with several MS poor outcomes and, in absence of universal health care, to reduced access to DMTs[70,71,72,73]. However, it should be noted that low socioeconomic status is also associated with many risk factors for health, which may drive the observed association and MS itself largely influences socioeconomic status[6]. Moreover, socioeconomic status, together with disability burden, impacts

access to health care outside MS therapy needs and it also influences access to food and exposure to toxicants and pollutants, thus exacerbating disparities[74,75,76,77]. Indeed, studies have identified air pollutants as possible risk factors for MS onset and relapses[78,79,80]. Finally another relevant issue of MS is the risk of reduced social participation and decreased in quality of life[81,82,83]. In this context, targeted interventions in terms of tangible and intangible social support may substantially contribute to improve quality of life[6].

In conclusion, social determinants of health drive large inequalities that result in worse MS related outcomes and MS itself possibly negatively influences non-static SDOH. Even if addressing non-medical factors related to individual and societal context seems outside the responsibilities of neurology, it is now clear the relevance of SDOH to achieve best health care and outcomes. It is thus essential to assess SDOH in MS research and clinical practice, to identify potential poor determinants and act on possible modifiable factors[6].

Projects on MS and inequalities

This section presents three projects which study inequalities in MS from different perspectives. First, an article on racial and ethnical representativeness in MS phase 3 clinical trials highlights the need of more accurate and inclusive reporting of race and ethnicity (first author)[8]. Second, a simulation study on strategies to study race in the environmental justice context is presented, with special emphasis on analytical approaches. This work is still under internal revisions and will be submitted soon, with me as the first author. Finally, the SocialMS project is introduced. It is a cross-sectional study to explore SDOH in the Italian MS context. I personally worked on both conceptualization of the study and data analysis.

Race and ethnicity in multiple sclerosis phase 3 clinical trials: A systematic review[8]

MS is a global disease which is not rare in Black people. In this context, it is essential for clinical research to be generalizable to the overall population, including disadvantaged groups based on race, ethnicity and other SDOH. However, in MS clinical trials the representativeness of individuals treated in clinical practice is seldom met. In particular, phase III clinical trials often lack of diversity, which is a multidimensional construct including race and ethnicity. Recent years have seen an increasing awareness on the relevance of diversity and on the need of more efforts also at the enrollment phase. Specifically, sponsors of randomized clinical trials are now required to submit a race and ethnicity diversity action plan and current recommendations suggest to always report information on race and ethnicity, possibly using the Clinical Data Interchange Standard Consortium (CDISC). Additionally, based on a regulation effective from January 18 2017, race and ethnicity, if collected, need to be reported in the results section of *ClinicalTrials.gov*, using customized categories or standard National Institutes

of Health (NIH)/Office of Management and Budget (OMB) classifications (Race: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Black or African American, White, more than one race, and unknown or not reported; Ethnicity: Hispanic or Latino, not Hispanic or Latino, and unknown or not reported). However, it must be noted that race and ethnicity classifications commonly used in the United States can be meaningless or inaccurate elsewhere. A systematic review explored race and ethnicity reporting in MS phase III randomized clinical trials assessing FDA-approved DMTs, retrieving information from PubMed and DMTs websites. Of 45 trials, only 62.2% reported any details on race or ethnicity and 31.1% reported the percentage of White individuals only. When information was reported, the median percentage of White participants was 93.8%, compared to only 1.9% of Black and 0.5% of Asian. This review surely offered an useful starting point but only DMTs approved before 2020 were considered and only published material was explored, without using for *ClinicalTrials.gov.* Here, we provide a more comprehensive review of race and ethnicity representation in phase III randomized clinical trials, including the studies registered with results on *ClinicalTrials.gov* that started from September 27, 2007 (date of the FDA amendments act) and were completed or terminated by December 31, 2023. First we aim to explore whether race and ethnicity were reported in *ClinicalTrials.gov*, also distinguishing between pre and post 2017 requirement. Next, we want to describe how data were reported and to evaluate representativeness of racial and ethnical groups. Finally, we will make comparisons with the corresponding publications, if available.

After having defined the search string, two authors independently identified the eligible clinical trials on *ClinicalTrials.gov* and excluded the studies enrolling patients without MS. In the included studies, we searched for race and ethnicity information on *ClinicalTrials.gov* and we extracted other information on the study, including title of the study, arms, eligible age, dates of start, completion and primary

completion, locations were the study was conducted and region of enrollment. Next, the corresponding publications were identified searching for the National Clinical Trial (NCT) number on *PubMed*, directly on *ClinicalTrials.gov* and using a machine learning-based web tool. Even if no effects of interventions were explored, guidelines from the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) were followed, to ensure transparency, completeness and accuracy.

After 8 exclusions, a total of 99 clinical trials were included. The studies started between 2007 and 2020 and were completed between 2009 and 2023. Fifty-eight trials were primarily completed before January 18 2017 (pre-requirement). Race or ethnicity were reported in 55 studies, of which 15 pre-requirement. Post-requirement only one study did not report race or ethnicity, meaning that the information was not collected. A total of 33,891 participants were included in the 55 studies reporting any information on race or ethnicity (median of 402, IQR=136-1047). Region of enrollment was reported only for 18 studies (6536 patients) and 60% were enrolled in Eastern Europe. Most of the patients (93%) were White; median percentage of White participants across studies was 93.2% (IQR=86.3%-98.3%, across 54 studies) compared to 3.1% for Black patients (IQR=0.7%-11.6%, across 54 studies) and 0.2% for Asian subjects (IQR=0%-1.4%). Median frequencies of White participants pre- and post-requirement were respectively 97.2% (IQR=93.8%-98.4%) and 90.0% (IQR=84.9%-98.1%). One study reported ethnicity but not race while 28 trials reported only race. Race was directly expressed using NIH/OMB standard classifications in 24 trials and for six studies frequencies of standard categories could be derived, resulting in a total of 9131 subjects (American Indian or Alaska Native: 11 (0.1%), Asian: 87 (1%), Native Hawaiian or Other Pacific Islander: 3 (0.0%), Black or African American: 388 (4.2%), White: 8282 (90.7%), more than one race: 23 (0.3%), unknown or not reported: 337 (3.7%)). In the remaining studies customized categories were often used to add the

‘Other’ class (23 studies). Concerning ethnicity, 16 trials directly followed the NIH/OMB standards and seven studies distinguished between ‘unknown’ and ‘not reported’ resulting in a total of 10,068 participants (Hispanic or Latino: 347 (3.4%), not Hispanic or Latino: 9398 (93.3%), unknown or not reported: 323 (3.2%)). As a subgroup analysis, when data on country of enrollment were available and patients were uniquely enrolled from a single country, race and ethnicity results were combined with region of enrollment. Only nine studies were included, eight from the United States and one from Eastern Europe. All the participants enrolled in Eastern Europe were White, compared to 85% of those enrolled in the United States. For 32/55 (58%) studies the corresponding publications were identified but only 24 (75%) reported information on race or ethnicity (6/11 (55%) pre-requirement and 18/21 (86%) post-requirement). Race and ethnicity were completely omitted for four trials (3 pre-requirement), with percentages of White participants ranging from 94.9% to 99.8% and other four studies reported race or ethnicity only in pooled analyses, combining participants of two trials. Even when race or ethnicity were reported in both the sources, some differences in terminology were observed (African vs African Descend, Black vs Black or African American, Black or African American vs African descended, Black or African American vs African American; American Indian vs Native American; White vs Caucasian, White vs White/Caucasian). Additionally, in the corresponding publications, categories with few participants were often collapsed into the ‘Other’ or ‘Non-White’ category or a different categorization was used. On the other hand, only few articles reported ethnicity information, even if it was reported on *ClinicalTrials.gov* while two publications reported ethnicity details that were not originally reported in *ClinicalTrials.gov.*

This review identified that only 56% of the studies reported race or ethnicity information on *ClinicalTrials.gov*. However, it is encouraging to know that almost all the post-requirement trials reported details on race or ethnicity. Collecting and

reporting race and ethnicity is necessary to guarantee transparency to representativeness. Consistently with previous results, when race or ethnicity information was available, most of the participants were White and not Hispanic or Latino. This means that minoritized groups receive treatments based on studies that clearly fail to adequately represent them. According to a systematic review of 44 articles, barriers to research participation include lack of access to information, health insurance and legal status. More efforts are thus necessary, at a design phase, to address SDOH that historically limit the enrollment of underrepresented populations, as it was done for the CHIMES study. Notably, we observed an increase in representativeness over time, probably due to growing awareness of the relevance of diversity. A strength of this study was the focus on terminology, observing high heterogeneity even within the same study. For example, 'Caucasian' was often used as a synonym of White but technically describes populations from the Caucasus and it has deep racist roots. Moreover, publications often collapsed minoritized groups into the 'Other' or 'Non-White' category. In this context, accurate word choice and completeness is essential to provide detailed information and to convey respect. Additionally, the picture is even more complex due to inaccurate or incorrect reporting of race or ethnicity. First, differences could occur between self-reported and electronic health record responses. Second, categorizations used in the United States may be meaningless or inaccurate elsewhere. That's why recent recommendations suggested to follow the CDISC reporting approach, to meet global needs while still adhering to standards. However, in this review we unexpectedly observed that customized categories were never used to ensure more granularity but to include the 'Other' category. This review has some limitations. First, no additional information such as sociodemographic factors were explored. Second, combined data on race/ethnicity and region of enrollment were not reported and we could only perform a subgroup analysis including very few participants. Third, the methodology used to collect

data on race and ethnicity was not reported in *ClinicalTrials.gov* and was detailed only rarely in publications. Fourth, only trials with results in *ClinicalTrials.gov* were included, which may possibly lead to bias. However, the use of *ClinicalTrials.gov* as the main source was actually one of the main strengths of this work, allowing to address reporting bias. Interestingly, the four studies that completely omitted race and ethnicity information, enrolled almost only White individuals, which may suggest a potential influence of poor diversity on the selective non-reporting of race and ethnicity. In conclusion, this review highlighted the need of more efforts at a publication phase as well as at a design phase to guarantee accurate collecting and reporting of race and ethnicity and to ensure generalizability of results.

Statistical considerations for environmental racism: strategies for evaluating race as a proxy in environmental justice research

People from marginalized groups, especially based on race or ethnicity, are more at risk to be exposed to environmental toxicants associated with worst health outcomes. Epidemiology has largely discussed analytical approaches to quantify and address racial disparities and recent publications have investigated the integration of causal inference in health disparities research. However, the majority of the studies still use the variable ‘race’ with little or no unpacking, as primary variable of interest in regression models, as an adjustment covariate or as an effect modifier. In the context of racial disparities, racial differences in environmental exposures and associated health outcomes are often seen as deterministic. However, it is well known that the variable ‘race’ is a social construct due to complex historical and societal factors rooted in systemic racism and analytic approaches should take this into account. In particular, to achieve health equity, the variable ‘race’ should be unpacked and we need to test possible ways in which environmental racisms operates, with the final goal of developing interventions on

the modifiable risk factors. Unpacking the processes that drive the disparity results in better model specification, study design, causal assumptions, interpretation of results and identification of interventions. However, a critical aspect is to avoid incorrect assumptions on the causal effect of race. In this commentary, we discuss how to address common research questions in environmental epidemiology without making deterministic assumptions of causality on race. Specifically, race itself is not a cause of environmental exposure disparities and specification of potential mechanisms by which racism operates is essential to identify possible solutions.

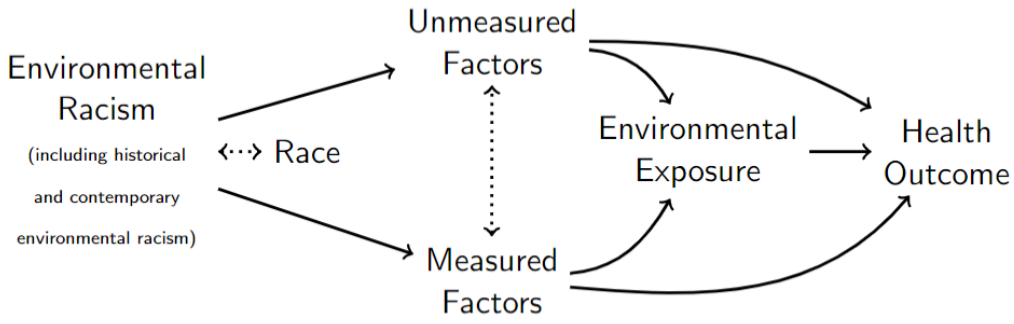

Figure 1. Basic conceptual diagram for evaluating the impact of environmental racism on health disparities. Heterogeneous exposures to environmental factors (e.g. air pollution, chemicals, metals, etc.) and health outcomes are due to a set of social, behavioral, and historical factors, associated with the social construct "race" through structural racism. Based on study-specific characteristics, some of these factors will be available to the researchers (measured factors), and others will be unavailable or unknown (unmeasured factors). Dotted lines signify associations and not causal effects.

Figure 1 represents a basic conceptual diagram for racial environmental health disparities. It is reasonable to assume that it is a set of racism-related factors that influence exposures and health outcomes. We assume no direct causal effect of race on environmental exposure and health outcome while disparities are due to social

and historical factors rooted in racism that influence living place, access, availability, behavior, lifestyle factors. This means that race is associated with both exposures and outcome but only through pathways operating through racisms. This diagram shows a general and basic structure which should be enlarged and applied to the specific contexts.

In this commentary, as an illustrative example, we considered the role of environmental racism on the risk of low birth weight (BW) among non-Hispanic Black individuals compared to non-Hispanic White, with special emphasis on exposure to Monoethyl phthalate (MEP) as a partial contributor to the racial environmental health disparity. MEP is the biologically-active metabolite of diethyl phthalate, which is mostly used in personal care products. Studies have found the following associations: a) higher concentrations of certain phthalates and lower BW; b) higher use of certain personal care products (i.e. hair oils and perfumes) and higher concentrations of MEP; c) higher use of hair oils and lower BW. In this context, beauty standards largely contribute to racial disparities, with targeted marketing and overabundance of personal care products containing phthalates in Black communities. Figure 2 represents the diagram corresponding to the illustrative example.

The diagram includes not only individual drivers of the associations but also the community ones (e.g. targeted marketing and neighborhood accessibility of safer products). Additionally, also other unmeasured alternative pathways may exist and interact with the measured one.

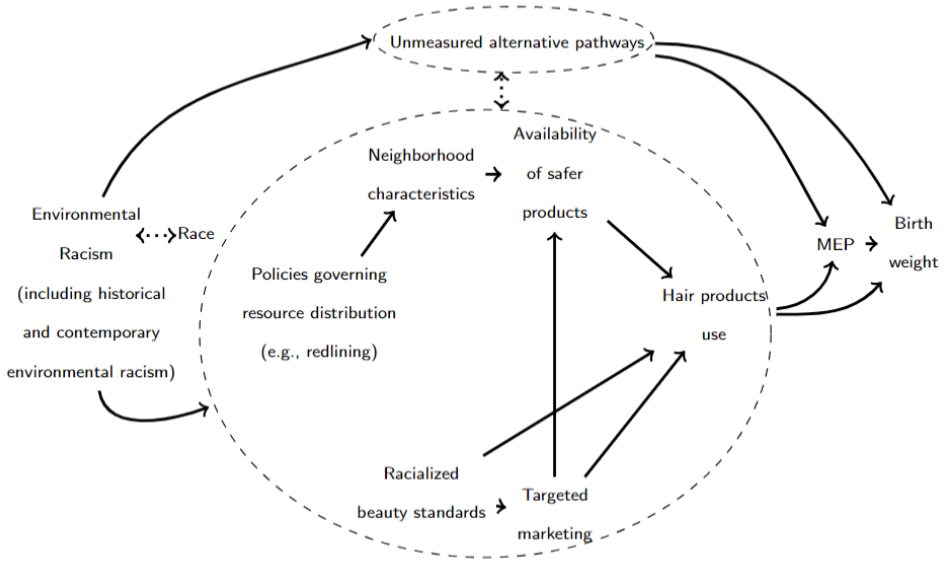

Figure 2. Conceptual diagram for racial environmental health disparities in Monoethyl phthalate (MEP), birth weight (BW), and the contribution of racism-induced differences in hair products usage. Dotted lines signify associations and not causal effects.

To present analytical steps, we simulated a sample of 10,000 subjects based on associations from the literature, simulating two main different scenarios: where the environmental health disparity is explained by mostly measured factors and where it is explained by both measured and unmeasured factors. Firstly, the first scenario was simulated. Race was simulated based on a Bernoulli variable with parameter 0.19. Use of hair products containing endocrine disruptive chemicals (EDCs) was simulated as a Bernoulli variable with parameters of 0.494 (race B) and 0.077 (race A). Unmeasured factors were quantified as a normal continuous variable with standard deviation 3 and with means 4 (race B) and 0 (race A). MEP urinary concentration was defined as a normal variable with standard deviation 12 and with mean defined as $\beta 0+\beta 1$(use of hair products containing EDCs)+ $\beta 2$(other unmeasured factors)+ $\beta 3$(interaction between hair products and other unmeasured

factors), with β0, β1, β2 and β3 respectively set to 61, 20, 0.1 and 0.5. BW was simulated as a normal variable with standard deviation 450 and with mean defined as α0+ α1(2nd quartile of MEP) +α2(3rd quartile of MEP) +α3(4th quartile of MEP) +α4(use of hair products containing EDCs) +α5(interaction between hair products use and MEP) + α6(other unmeasured factors)+ α7(interaction between hair products use and other unmeasured factors)+ α8(interaction between other unmeasured factors and MEP), with α0, α1, α2, α3, α4, α5, α6, α7, α8 respectively set to 3490, -34.6, -200.2, -72.1, -54, -2, -2, -0.5, -0.005. This scenario was replicated 1000 times and average estimates were calculated. The scenario where disparity was largely due to unmeasured factors was simulated based on the following modifications: α6 set to -5, β2 set to 1.5, β3 set to 1, α7 set to -2 and α8 set to -0.05. Next, three steps were defined in order to quantify the environmental health disparity of interest in simulated data. Specifically, to study, describe and estimate the magnitude of the disparity it is essential to: 1) explore differences in the racial distribution of the environmental exposure, 2) investigate differences in the racial distribution of the health outcome, 3) estimate the effects of the environmental exposure on the health outcome over subpopulations of interest. Figure 3 summarizes results of these three steps in simulated data, showing higher distribution of the MEP and lower BW in the historically marginalized group (race B). The association between MEP on BW showed a 23% greater reduction in BW in individuals of race B (-6.12 g vs -4.97 g).

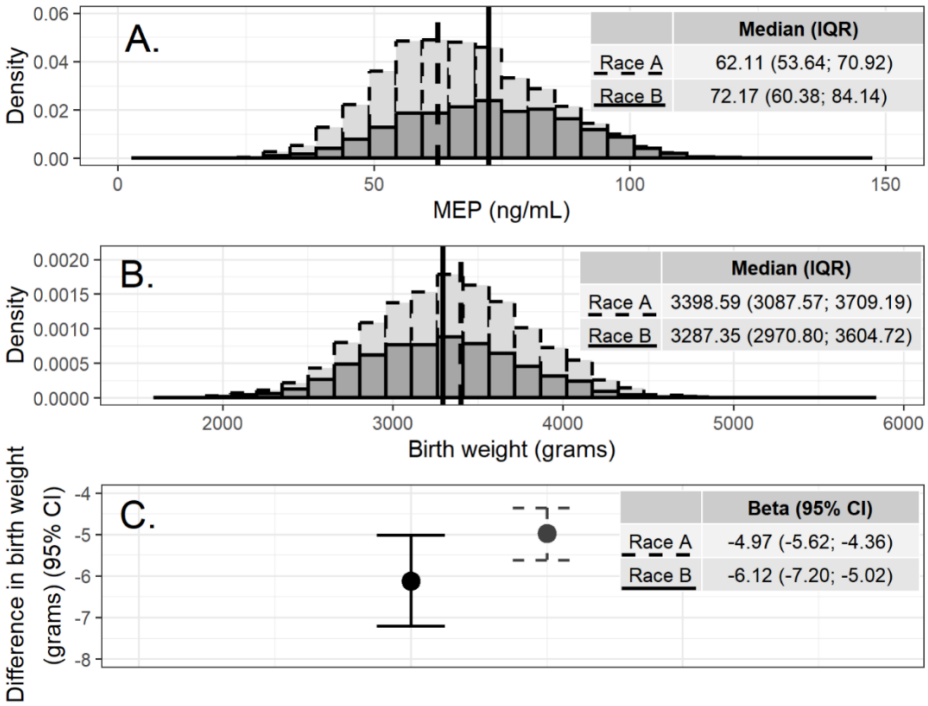

Figure 3. Analytical steps to describe and quantify the environmental health disparity in the simulated dataset: explore differences in the racial distribution of the environmental exposure (A); investigate differences in the racial distribution of the health outcome (B); estimate the effects of the environmental exposure on the health outcome over subpopulations of interest (C).

Next, we incorporated race in the exposure-outcome association as a confounder. Confounders are variables associated with both the exposure and the outcome which are not a part of the causal pathway and that must be used to block alternative pathways that can lead from exposure to outcome. We simulated several sets of adjustment as compared to the real effect (adjusting for both measured and unmeasured factors) (Figure 4).

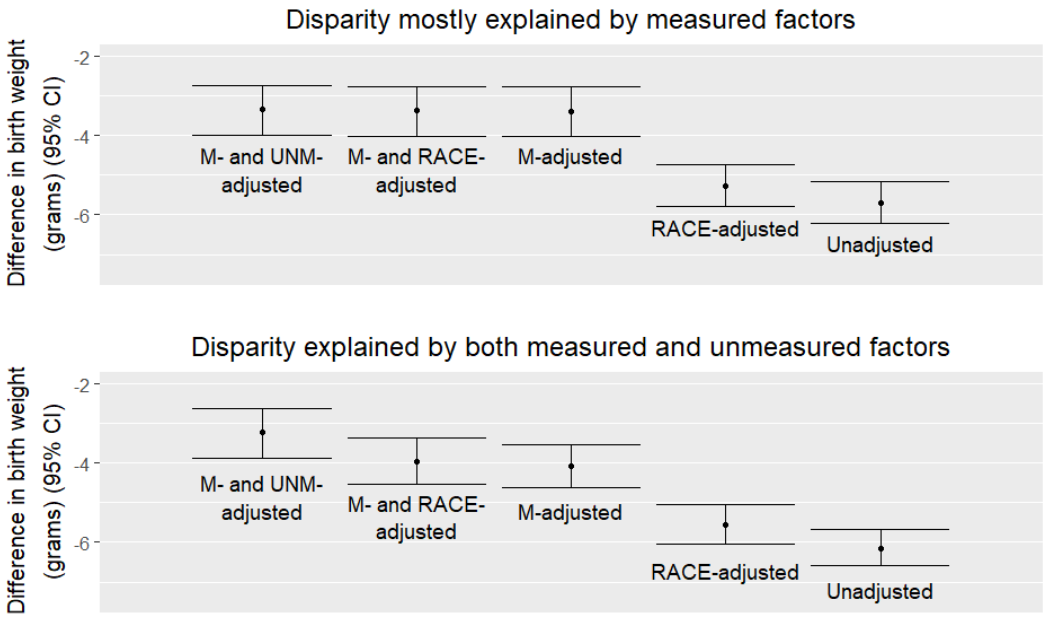

Figure 4. Estimates of the overall effect of MEP on BW in the simulated data under several adjustment sets. M-Measured factors; UNM-Unmeasured factors.

In both scenarios, adjusting for race alone led to estimates close to unadjusted models. Adjusting for measured factors was a better option even when unmeasured factors considerably contribute to the disparity. Further inclusion of race only slightly improved the precision of the estimate. To improve precision, we can still incorporate race in the model as a confounder but in order to largely reduce bias it is essential to appropriately specify what race means and how racism is operating.

In this commentary we highlighted the importance of accurately defining a conceptual diagram to detail downstream and upstream factors that explain environmental racial disparities. We also outlined some basic analytical steps to quantify and study environmental disparities and we showed that, especially when unmeasured factors are influent, race could be still included as a confounder. This study has some limitations. First, we did not address mediation analysis and causal decomposition. Second, future research should also investigate the issue of

measurement error, which can possibly differentially affect strata of the populations. In conclusion, race still remains a critically important variable but it is essential to accurately unpack what race and racism mean and to correctly specify analytical models.

A comprehensive overview of social determinants of health among patients with Multiple Sclerosis in Italy: the SocialMS study

In Europe, Italy is characterized by relevant regional health disparities and SDOH distribution has largely changed in the past years. Some studies have explored SDOH in Italian MS patients but just focusing on single determinants such as gender and sexual orientation, employment, education, socioeconomic status, food habits, air pollution and social support. However, there is a need for a comprehensive study that measures and relates several SDOH simultaneously and that also explores the impact of MS itself on SDOH. The aim of this study is to provide a comprehensive overview of the distribution of SDOH in patients with MS living in Italy, overall and by geographical area. Specifically, we aim 1) to study the distribution of each single SDOH and to explore the interrelationships, 2) to assess the impact of MS on non-static determinants, 3) to study the association between SDOH and MS-related outcomes. A comprehensive overview of the current Italian situation can surely help to identify potential issues and to direct future interventions, both at territorial and individual levels.

This is an observational cross-sectional study and data were collected through a self-administered anonymous online survey (approval of the ethical committee n. 2023.96, received on December 22, 2023). Only adults patients diagnosed with MS were eligible and we excluded patients not providing consent to participate and those who skipped the SDOH section in the questionnaire. The questionnaire was structured in three sections, on demographic and MS characteristics and on SDOH, with a specific subsection for each SDOH (gender and sexual orientation,

geographical origins, education, working, socio-economic status, abuse, transportation and access to care, food, air pollution and social support). According to proportional allocation sample size calculation, a total of 427 participants were required (North: n=197, Center: n=85, South and Islands: n=145). The survey was developed in REDCap at the University of Genoa and patients could access via an online link or QR-code. To promote the participation in the study, the Italian Association on Multiple Sclerosis (AISM), several Italian MS centers and neurologists were contacted and official posters and flyers were provided. All the material was supported by a brief explanation of rational and objectives of the study, and e-mail contacts of the SocialMS study group were provided to patients. Questions were defined by an interdisciplinary team and in case of disagreement, questions were discussed to reach a consensus. Disability was assessed as patient determined disease step (PDDS) and several other information of MS course were self-reported by the patients. To derive SDOH, we took into consideration the distinctive features of the Italian context while inspiring from available validated questionnaires (Health Leads' toolkit). Data collection started on February 20, 2024 and closed on 31 October 2024. As of August 17, 2024 a total of 1461 patients participated, resulting in a total of 1090 patients after exclusions (37% Northern, 29% Central and 34% Southern Italy and Islands); 68% were females and median age was 44.17 (range: 18.53-84.84). PDDS ranged between 0 and 8 (Median=1, IQR=0-3); PDDS was greater for patients with financial difficulties (17%) (β=0.97, $p<0.001$) as well as for those without a college degree (62%) (β=0.39, p=0.001); lower education was associated with both poorer economic status and unemployment ($p<0.001$). Financial difficulties were associated with longer months between MS symptoms and diagnosis (median, IQR: 6, 3-15 vs 4, 1-12; p=0.002) and diagnostic delay was associated with greater disability (>4 months: β=0.49, $p<0.001$). Notably, long waiting lists were a common issue for access to care and patients who could afford private healthcare (59%) were those with greater

income, higher education and with medical insurance ($p<0.001$). Interestingly, MS itself was found to have a negative impact on many SDOH: 1) educational goals (40%), 2) professional goals (45%), job quit/change due to MS diagnosis (12%) or disability (16%), 3) financial resources (33%), 4) abuse (3%), 5) social life (44%), relationship with the partner (31%) and with friends (23%). Notably, the impact of MS was even stronger for more disabled patients.

Conclusions

In this thesis, a collection of projects on MS were presented, mainly focusing on three themes: 1) COVID-19 infection and pandemic, 2) treatments and study design, 3) SDOH and inequalities. These three subjects are highly interrelated. In particular, at the beginning of the pandemic, COVID-19 raised additional concern within the population of MS patients mainly because DMTs influence immune response, making patients more susceptible to infections. Indeed patients under anti-CD20, especially Rituximab, were found to be at higher risk of severe COVID-19 course. Additionally COVID-19 pandemic negatively impacted many social determinants of health, further exacerbating health inequalities. Finally, there exists a close link between treatments and inequities, in terms of representativeness in clinical research as well as in early access to therapies.

Most of the works on COVID-19 were conducted in the context of the MuSC-19 study. Specifically, findings from the MuSC-19 Egyptian cohort highlighted headache as a risk factor for COVID-19 severity which can potentially be specific of the Egyptian context while no associations with DMTs were observed, probably due to low power. On the other hand, two articles focusing on air pollution showed higher PM2.5 concentrations as a co-factor for COVID-19 severity and identified PM2.5, PM10 and NO2 as risk factors for pneumonia, both individually and as a mixture, with results principally driven by NO2 and PM2.5. MuSC-19 data were also used to construct a multiparametric score to assess the individual risk of severe COVID-19, using several statistical approaches. Despite the modest predictive ability and lack of external validation, the tool could be useful to identify high risk patients and recommend important prevention measures. The majority of the studies confirmed anti-CD20 therapy as a risk factor for COVID-19 severity. The

systematic review on severe COVID-19 outcomes under anti-CD20 therapies identified patients treated with Rituximab to be at higher risk of death (pooled mortal rate estimate: 1.8% overall vs 4.5% under Rituximab). Although much effort, especially at the beginning of pandemic, has been directed to identify demographic and MS-specific risk factors for worse COVID-19 course, research also focused on prevention, as demonstrated by the three surveys. In particular, we introduced a score to quantify adherence to lockdown recommendations, showing overall good adherence but highlighting the influence of cohabitants' working modalities and the need of more social assistance. We also explored patients' point of view in the use of telemedicine, showing that more than half of participants were open to this modality, especially those with higher income, living further from the MS centre, using computers/tablets and navigating the Internet for remote activities. However, for most of the patients telemedicine was found useful as an occasional tool and many efforts are still necessary to improve technological skills of the patients. On the other hand, also the digital work engagement of Italian neurologists during the pandemic was explored. In particular, we found that 48% of neurologists - especially those with older age, and not from North Italy - communicate with patients using social media, principally via WhatsApp. The survey also revealed the issue of fake news circulating online and the efforts made to direct patients to reliable sites. To conclude, these studies on COVID-19 explored risk factors for severe course of infection in still unexplored settings or using advanced statistical methodologies. Additionally, findings from the three surveys showed attitudes and opinions of both patients and neurologists during the pandemic, which could be useful to direct future interventions, also outside the pandemic period.

Two articles were presented in the section on treatments, both with focus on advanced statistical methods and study designs. First, the TRANSFORMS trial was emulated according to appropriate methodology, leading to estimates similar to the original trial. Next, the Bayesian approach was applied in a pediatric clinical trial

to overcome sample size issues. These two articles highlighted the relevance of real-word evidence under rigorous methodology and the utility of advanced statistical approaches to solve issues typical of standard study designs.

In the last section, the systematic review highlighted the need of more efforts, both at a publication and at a design phase, for accurately reporting race and ethnicity and for ensuring representativeness to minoritized racial and ethnical groups. The simulation study provided a toolkit for analytically studying the variable ‘race’, recommending to construct a conceptual diagram that adequately represents the causal pathways responsible of the health disparity. Race remains still a relevant variable but it is essential to unpack its meaning in relation with historical and contemporary racism. Finally, the SocialMS study aims to simultaneously explore several SDOH in the Italian MS context. The first results highlighted interrelations among SDOH, their impact on MS-related outcomes and the negative influence of MS itself on worsening of social determinants. This study will provide useful evidence to guide future interventions, at individual and territorial levels.

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