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The Impact of the COVID-19 Pandemic on People with Multiple Sclerosis

PhD

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Declaration

I hereby confirm that the present thesis, 'The Impact of the COVID-19 Pandemic on People with Multiple Sclerosis', is the result of my independent scholarly work and that in all cases material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, and quotations and paraphrases are clearly indicated. No material other than that listed has been used. I have read and understood the Institute's regulations and procedures concerning plagiarism.

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To Mahlisha

with all my love

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Abbreviations

ABN	Association of British Neurologists
aHR	Adjusted Hazard Ratio
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DAG	Directed Acyclic Graph
DCT	Decentralised Clinical Trial
DMT	Disease-Modifying Therapy
GAD-7	General Anxiety Disorder 7-item
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale for Anxiety
HADS-D	Hospital Anxiety and Depression Scale for Depression
IES-R	Impact of Event Scale—Revised
IQR	Interquartile Range
IRB	Institutional Review Board
IRR	Incidence Rate Ratio
LFT	Lateral Flow Test
LOT-R	Revised Life Orientation Test
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29v2	Multiple Sclerosis Impact Scale version 2

NHS	National Health Service
NHSE/I	NHS England and NHS Improvement
OR	Odds Ratio
PHQ-9	Patient Health Questionnaire 9-question
PMS	Progressive Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PTSD	Post-Traumatic Stress Disorder
RAT	Rapid Antigen Test
RCT	Randomised Controlled Trial
RRMS	Relapsing-Remitting Multiple Sclerosis
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Distress Syndrome-Coronavirus-2
SD	Standard Deviation
SpINDLE	Spinal Cord Imaging in Neuropathy of Diabetes: Longitudinal Evaluation
SPMS	Secondary Progressive Multiple Sclerosis
UKHSA	UK Health Security Agency
UKMSR	UK MS Register
WebEDSS	Web-Based Expanded Disability Status Scale

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Abstract

The interplay between multiple sclerosis (MS) and the coronavirus disease 2019 (COVID-19) was unknown when I started my PhD research on this topic. MS is a chronic inflammatory disorder of the central nervous system that can impair physical and mental health. The risk of contracting COVID-19 and its course in people with MS and the effect of MS-specific factors, such as physical disability, on them were unknown. Infections were known to exacerbate MS symptoms, but the effect of COVID-19 on the disease course of MS was unclear. Several people with MS are treated with immunomodulatory disease-modifying therapies (DMTs). There were concerns about the risk of COVID-19 associated with these DMTs and the response to COVID-19 vaccines in this population.

I show that, before the COVID-19 vaccination programme, people with MS were not at an increased risk of contracting COVID-19 compared to the general population and none of the MS-specific factors increased this risk. People on ocrelizumab and fingolimod did not respond to COVID-19 vaccines and were at increased risk of contracting COVID-19. People with MS can take longer to recover from COVID-19, especially if they have higher levels of physical disability, have anxiety or depression, or are female. COVID-19 can exacerbate MS, but DMTs seem to prevent infection-related new MS symptoms. People with MS remained at high risk of having anxiety or depression during the pandemic and were affected more

adversely by the impact of the pandemic on lifestyle and social determinants of mental health.

The COVID-19 pandemic also forced the academic community to adopt different and at times, innovative research methodologies. These techniques form parts of decentralised clinical trials (DCTs). I have reviewed the literature on the use of DCTs in MS research.

Overall, my research provides valuable insights into the impact of the COVID-19 pandemic on different aspects of the lives of people with MS. The findings can be used to inform the development of more personalised care for people with MS and have implications for future MS research.

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Chapter 1

Preface

1. Preface

1.1. COVID-19 Impact Statement

In this thesis, I hope to have painted a picture of how the coronavirus disease 2019 (COVID-19) pandemic impacted various aspects of the lives of people with multiple sclerosis (MS), but within it also lies a story of how the pandemic shaped the course my research toward a PhD degree. In a time when the COVID-19 pandemic had adversely affected research activities in the UK and worldwide,[1-3] including my planned research project (Spinal Cord Imaging in Neuropathy of Diabetes: Longitudinal Evaluation [SpINDLE]; ISRCTN11328492; see my first-year report for confirmation review in Appendix 1-A), I happened to be in a place with people who were able to come together with others across the UK to repurpose established MS research resources (e.g., the UK MS Register: https://ukmsregister.org; UKMSR) as well as potential ones (e.g., the National Health Service [NHS] England data held by the Arden & GEM Commissioning Support Unit: https://www.ardengemcsu.nhs.uk) for COVID-19 research in this population. My aspiration to do impactful research led to the decision to drastically change my research field to MS and COVID-19 when it was needed the most. This change provided me with several learning opportunities in the process.

I worked closely with experts in a wide range of disciplines—from neurologists to psychologists, psychiatrists, and pharmacists, from data managers and analysts to statisticians, and from clinicians and academics

to charities and people with MS. These interactions, which were required quite frequently as the COVID-19 pandemic unfolded and were facilitated by online communications without the restrictions of time and place, helped me understand *how* these experts think in the process of research in addition to *what* they think. I went through all phases of a research project—from planning to conduct, data analysis and interpretation, and presentation of the findings, many times within a limited period and under the pressures of a pandemic that was affecting our personal and professional lives. We published our unique experience of working together as a team in such uncertain times on a rapidly evolving topic as an autoethnographic study.[4] Moreover, the COVID-19 pandemic and the changes it imposed on different stages of research highlighted how it can benefit from different methodologies, so I proceeded to review the literature on facilitating remote clinical trials in MS. This topic is covered in Chapter 8 of this thesis.

This thesis is, therefore, a direct result of a global health crisis that impacted the lives of the researchers and research participants. I hope that the work of this thesis improved the lives of people with MS in those difficult times and will continue to exert a positive effect on their care in the future.

1.2. COVID-19 Research in MS

1.2.1. COVID-19 Timeline

COVID-19 raised concerns around the globe since its outbreak in December 2019.[5] The World Health Organization declared COVID-19 as a pandemic on 11th March 2020.[5]

In the UK, the first case of COVID-19 was reported in February 2020.[6] With the rising number of cases, the first national lockdown ensued in March 2020.[6 7] Following the lockdown, there was a decline in COVID-19 rates, which resulted in easing of the restrictions in June 2020.[7] A few national COVID-19 restrictions (e.g., social distancing, the 'Rule of six') and a series of local lockdowns, however, were enforced to contain the spread of infection.[7] The next national lockdowns took place in November 2020 and January 2021.[7] With the roll-out of the COVID-19 vaccination programme in December 2020 and its exceptional uptake by the general population, there was no need for further lockdowns—the programme successfully resulted in a steep decline in COVID-19-related hospital admissions and deaths.[8]

In the beginning, COVID-19 testing in the UK was limited to suspected cases admitted to the hospital and was done using reverse transcriptase polymerase chain reaction (RT-PCR).[9] In April-March 2020 mass community COVID-19 testing, using RT-PCR, was established.[9] As COVID-19 lateral flow tests (LFTs) were developed, their use gradually took over RT-PCR for

almost all asymptomatic infection tracing and most mildly symptomatic infections by March 2021.[9]

1.2.2. The MS Population

In 2016, it was estimated that over two million people lived with MS, globally.[10] More than 100,000 people with MS were living in the UK in 2018 and almost 5,000 new cases were being diagnosed each year.[11]

MS is a chronic inflammatory disorder of the central nervous system,[12] which can impair—to varying extents, the physical as well as psychological health of affected people.[13] [14] People with MS form a large population who receive immunomodulatory treatments, referred to as disease-modifying therapies (DMTs).[15] In the UK, over 21,000 people with MS are on DMTs.[15]

The following sections will present the concerns that were raised by the COVID-19 pandemic in this MS community.

1.2.3. MS, a Chronic Neurological Disease

People with MS were known to be at increased risk of infections and hospitalisation as a result of these infections, even before the COVID-19 pandemic.[16] When the COVID-19 pandemic started, it was unclear whether MS—as a chronic disease that can cause significant neurological disability, would increase the risk of contracting COVID-19 or its severe outcomes (i.e., hospitalisation or death) like frailty or other chronic conditions (e.g., chronic pulmonary, heart, or kidney disease) could.[17] [18]

In this thesis, I have studied the risk of contracting COVID-19 in people with MS and compared them to populations without MS—before and after implementation of the COVID-19 vaccination programme (See Chapters 2 and 7). I have also studied recovery from COVID-19, as a measure of its severity, in people with MS (see Chapter 4). This thesis, however, will not cover the relationship between MS and severe outcomes of COVID-19 in terms of hospitalisation or death.

1.2.4. MS Disease Modifying Therapies

At the beginning of the COVID-19 pandemic, assumptions about the risk of contracting COVID-19 and its severity in people with MS taking immunomodulatory DMTs were solely based on previous evidence (mostly from clinical trials of these DMTs) and experience around the risk of other infections in this population.[19 20] Studies prior to the COVID-19 era suggested that MS DMTs are generally associated with an increased risk of infection.[21]

Beta-interferons and glatiramer acetate held the lowest risk of infection among MS DMTs.[21 22] Most other DMTs were known to predispose people with MS to various types and severities of infections as a result of different mechanisms and degrees of immunosuppression.[19 20] However, the theoretical risk of COVID-19 with most of these MS DMTs was not deemed high.[23-25] Interestingly, as beta-interferons were known to have some anti-viral properties,[23 25] they became a potential candidate for COVID-19

treatment in clinical trials;[26] they were shown to be inefficacious, however.[26] In another clinical trial (ClinicalTrials.gov: NCT04280588)—probably planned based on insufficient evidence,[23] fingolimod was considered for preventing acute respiratory distress syndrome in COVID-19 patients, because of its theoretical potential for suppression of the recruitment of monocytes and macrophages to the site of inflammation;[23] this study was prematurely stopped. These examples reflect the lack of understanding around the risk of COVID-19 associated with MS DMTs when the pandemic started.

Nonetheless, at the very early stages of the COVID-19 pandemic, national and international MS organisations, including the Association of British Neurologists (ABN), issued guidelines—based on available evidence, on MS DMT use during this period.[24 27] The general consensus was that ongoing treatment with MS DMTs should not be stopped.[24] When starting DMTs in treatment-naïve people with MS, however, it seemed preferable to avoid DMTs that cause significant immune cell-depletion, such as alemtuzumab, cladribine, or anti-CD20 monoclonal antibodies (e.g., rituximab or ocrelizumab).[24 25 27] Large-scale studies were required to ascertain the risk of COVID-19 associated with MS DMTs.[24 27]

The ground-breaking development of COVID-19 vaccines and their success promised an end to the COVID-19 pandemic.[8] However, people with MS on certain DMTs (namely sphingosine 1-phosphate receptor modulators such as fingolimod, anti-CD20 monoclonal antibodies, alemtuzumab, and

cladribine) faced new challenges as these DMTs could potentially suppress the COVID-19 vaccine response.[28]

My research has addressed some of the above concerns, which are presented in Chapters 2, 4, and 7 of this thesis.

1.2.5. MS Disease Course and COVID-19

Infections pose a risk of *relapse* in people with MS.[29-31] It is probably more appropriate to use the term *MS exacerbation* (or a similar term) rather than *relapse* for infection-associated new or worsening symptoms of MS, as the presence of infection defies the definition of an MS relapse.[32] Prospective longitudinal studies were required to follow up people with MS and COVID-19 and examine the effects of COVID-19 on their disease course. This topic is covered in Chapter 3 of this thesis.

1.2.6. Mental Health and Its Determinants in MS

There is a complex interplay between biological (e.g., genetics, physiology), psychological (e.g., thinking styles, personality), social (e.g., social support, financial stability), and lifestyle (e.g., smoking behaviour, exercise) factors that determine mental health outcomes.[33] Factors such as loneliness and reduced social support are known to adversely affect mental health and general wellbeing.[34 35] Times of uncertainty and unpredictability are also associated with increased symptoms of anxiety and depression.[36]

Anxiety and depression are common in MS,[14 37] and may be associated with worsening of MS symptoms.[38] Detection of anxiety and depression in people with MS is important so that they can be offered psychological and/or pharmacological interventions, which have proved effective in this population.[38-40] Addressing social determinants of mental health is also an important in the care of people with MS.[41]

The COVID-19 pandemic ushered in an era of uncertainty for everyone. However, it was possible that the pandemic would affect people with MS disproportionately because of the additional uncertainties in this population, as described in previous sections, or by imposing untoward changes in their lifestyle, social interactions, or employment/financial status. This topic will be addressed in Chapter 5 of this thesis.

1.3. Research Questions

The aim of this thesis is to present the impact of the COVID-19 pandemic on different aspects of the health and lives of people with MS. The research questions were developed as the COVID-19 pandemic unfolded, mainly through discussions with people with MS and health care professionals, and the studies were designed considering available resources to yield timely and high-quality results. These studies aimed to address the following research questions:

1. What is the association of MS and MS-related factors with the risk of contracting COVID-19?
2. Does COVID-19 vaccination alter the risk of contracting COVID-19 in the MS population on DMTs?
3. How did the COVID-19 pandemic affect the mental health of people with MS and its determinants?
4. What is the effect of COVID-19 on MS symptoms?
5. What is the course of recovery from COVID-19 in people with MS?
6. What is the current evidence on decentralised clinical trials in MS research?

1.4. Outline

Following this chapter, Chapters 2–5 will cover the studies designed and conducted within the prospective and longitudinal cohort of the UKMSR. Chapter 2 will present the rate of COVID-19 in a community-based MS population and the associations between MS-specific variables and the risk of contracting COVID-19. Chapter 3 will report the effects of COVID-19 on MS symptoms. Chapter 4 will present the course of recovery from COVID-19 in the MS population. Chapter 5 will address the effects of the COVID-19 pandemic on the mental health of people with MS and different aspects of their lives. Chapter 6 will discuss a relatively novel method of statistical analysis—in clinical research, that was used in the previous chapters. Chapter 7 will compare the rates of COVID-19 incidence before and after implementation of the COVID-19 vaccination programme in the MS and

general populations, using dispensing data of MS DMTs from the NHS England. Chapter 8 will review the literature on decentralised clinical trials in MS research. Chapter 9 will present a summary of this work in light of the above research questions and its potential impact on the care of people with MS and future MS research.

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Chapter 2

Self-reported COVID-19 in People with MS

2. Self-Reported COVID-19 in People with MS
A Community-Based Cohort of the UK MS Register

The published article is included in Appendix 2-A.[1] Following its publication, the study was updated and presented at the ABN Annual Meeting 2021.[2] These updates have been separately incorporated into the sections of the published article below. Given the unprecedented pace of COVID-19 research in the past four years, the relevant literature that emerged following the publication of this chapter will also be included.

2.1. Introduction

In the early phases of the UK COVID-19 outbreak, in the absence of clear evidence about the risks for people with MS and those taking immunomodulatory DMTs, we launched a community-based study as part of the UKMSR. We intended to capture the picture of COVID-19 among people with MS and their risk of contracting the disease. Here, we report our findings from 17th March to 24th April 2020.

2.1.1. Updated Report

The findings of this study were regularly updated to monitor the course of the COVID-19 pandemic in the MS community. The latest update covered the period from 17th March 2020 to 19th March 2021.

2.2. Methods

The COVID-19 study (clinicaltrials.gov: NCT04354519) is a prospective observational cohort study launched on 17th March 2020 as part of the UKMSR (Ethics: 16/SW/0194). People with MS (participants) completed a specific COVID-19 related survey which was combined with data held from before the pandemic where available. The primary outcome of the study is participant-reported self-diagnosis of COVID-19 (i.e., self-reported COVID-19). Participants were asked if their diagnosis was confirmed by testing—the available test in the UK, at the time, was RT-PCR. Participants reported if their sibling without MS, closest in age who was not living with them, had self-reported COVID-19. The likelihood of having COVID-19 was assessed using multivariable binomial logistic regression analysis with the variables: age, gender, ethnicity, MS duration and type, self-isolation and DMTs. DMTs were considered after stratifying based on moderate-efficacy versus high-efficacy therapies (as described in Table 2.1). Disability was assessed using the last recorded web-based Expanded Disability Status Scale (webEDSS) or MS Impact Scale version 2 (MSIS-29v2).[3] The results are reported as rates and odds ratios (OR) with 95% confidence intervals (95% CI).

2.2.1. Updated Methods

The initial statistical analysis involved a combination of clinical justification and backward elimination methods to determine the covariates of the multivariable binomial logistic regression analysis described above (section 2.2). This approach was modified in subsequent statistical analyses to avoid

data-driven results (further explained in Chapter 6). A causal model of the study variables was built (i.e., a Directed Acyclic Graph or DAG) and was used to determine the covariates of the regression analysis (Appendix 2-B).

The definition of confirmed COVID-19 was revised to include cases confirmed by RT-PCR, LFT, or a health care professional.

2.3. Results

As of 24 April, out of 3,910 participants, 237 (6.1%, 95% CI: 5.3–6.8%) had self-reported COVID-19 among whom 54 (22.8%, 95% CI: 17.5–28.2%) also had a diagnosis by a healthcare professional based on symptoms and 37 (15.6%, 95% CI: 11.2–20.6%) a confirmed diagnosis by testing. Three participants reported hospitalisation due to COVID-19. No deaths were reported.

Among 1,283 siblings without MS, 79 (6.2%) had a reported diagnosis of COVID-19. Adjusting for age and gender, the likelihood of contracting COVID-19 in people with MS was similar to siblings (OR: 1.180, 95% CI: 0.888–1.569).

Seven hundred and fifty-nine of 3,812 participants reported that they were self-isolating and that they had been self-isolating for at least 2 weeks before symptom onset if they had COVID-19. Of these, 2 (0.3%, 95% CI: 0–0.7%) had self-reported COVID-19 whereas 137 of 3,053 participants not self-isolating (4.5%, 95% CI: 3.8–5.2%) had the disease (p <0.001). Among participants with confirmed COVID-19, 94.6% (95% CI: 86.5–100%) were not self-isolating

which was higher than those without the disease (79.9%, 95% CI: 78.7–81.3%, p =0.023). Self-isolating participants were slightly older than those not self-isolating (p <0.001). A lower proportion of participants on DMTs were self-isolating compared with those not taking DMTs (18.1%, 95% CI: 16.4–20% vs 21.5%, 95% CI: 19.6–23.3%, p =0.01). Rate of self-isolation in participants taking high-efficacy DMTs was similar to those not taking DMTs and higher than those taking moderate-efficacy DMTs (21.3% vs 21.4% and 16.5%, p =0.993 and p =0.014, respectively). More participants with progressive MS (PMS) were self-isolating compared with relapsing-remitting MS (RRMS) (23.2%, 95% CI 21–25.3% vs 17.9%, 95% CI: 16.3–19.5%, p <0.001).

Using self-reported and confirmed COVID-19 as outcomes, 3,714 and 3,618 participants were included in the regression analysis, respectively. Self-isolation predicted a lower likelihood of having self-reported COVID-19 (OR: 0.064, 95% CI: 0.016–0.259) but not confirmed COVID-19.

Participants on DMTs were less likely to have self-reported COVID-19 (OR: 0.640, 95% CI: 0.428–0.957), which remained significant after removing self-isolating participants (OR: 0.633, 95% CI: 0.402–0.998). High-efficacy DMTs reduced the likelihood of self-reported COVID-19 compared with no DMTs (OR: 0.540, 95% CI: 0.311–0.938) but not compared with moderate-efficacy DMTs. There was no significant association between taking DMTs and having confirmed COVID-19. It was not possible to do a formal statistical test for the association between individual DMTs and COVID-19 due to small numbers (Table 2.1).

Table 2.1. Distribution of individual DMTs among participants of the COVID-19 study.

DMT	Total n (%) n = 3,907	Self-reported COVID-19 n (%) n = 236	Confirmed COVID-19 n (%) n = 37
None	2,088 (53.4)	116 (49.2)	11 (29.7)
Beta-interferons [a]	232 (5.9)	11 (4.7)	1 (2.7)
Glatiramer acetate [a]	196 (5)	18 (7.6)	3 (8.1)
Dimethyl fumarate [a]	446 (11.4)	32 (13.6)	7 (18.9)
Teriflunomide [a]	93 (2.4)	2 (0.8)	0 (0)
Fingolimod [a]	235 (6)	15 (6.4)	4 (10.8)
Siponimod	3 (0.1)	0 (0)	0 (0)
Ocrelizumab [b]	193 (4.9)	14 (5.9)	4 (10.8)
Natalizumab [b]	231 (5.9)	19 (8.1)	5 (13.5)
Cladribine [b]	73 (1.9)	2 (0.8)	0 (0)
Alemtuzumab [b]	93 (2.4)	5 (2.1)	2 (5.4)
HSCT [b]	2 (0.1)	0 (0)	0 (0)
Mitoxantrone [b]	0 (0)	0 (0)	0 (0)
Others [c]	16 (0.4)	2 (0.8)	0 (0)
Unknown	6 (0.2)	0 (0)	0 (0)

DMT = Disease-Modifying Therapy; HSCT = Haematopoietic Stem Cell Transplantation.

[a] defined as moderate-efficacy DMTs.

[b] defined as high-efficacy DMTs.

[c] Including Rituximab, Ofatumumab, Ublituximab, Vedolizumab, Ponesimod, Azathioprine, Mycophenolate Mofetil, and Methotrexate.

Younger age was associated with increased likelihood of having self-reported

(OR: 1.043, 95% CI: 1.022–1.064) and confirmed (OR: 1.048, 95% CI: 1.009–

1.087) COVID-19.

Participants with PMS were less likely to have self-reported (OR: 0.429, 95% CI: 0.241–0.763) or confirmed (OR: 0.119, 95% CI: 0.015–0.967) COVID-19 compared with those with RRMS, but this effect disappeared after excluding participants who were self-isolating.

Including webEDSS (n = 2,808) and physical MSIS-29v2 (n = 3,192) as additional predictors in the analysis showed no significant association with the likelihood of contracting COVID-19.

The gender distribution was similar between participants with and without COVID-19. More participants with self-reported COVID-19 reported themselves as having any ethnicity other than white compared with those without the disease (6.9%, 95% CI: 3.9–10.1% vs 3.8%, 95% CI: 3.2–4.4%, p = 0.019). Gender and ethnicity did not affect the likelihood of having COVID-19.

2.3.1. Updated Results

A total of 7,977 people with MS had participated in the study by 19th March 2021. One thousand ninety-five (13.7%) participants had self-reported COVID-19, with 356 (4.5%) having confirmed COVID-19. Twenty-four participants had been hospitalised due to (confirmed) COVID-19. The risk of contracting COVID-19 in this population is presented in Table 2.2.

***Table* 2.2.** Results of the multivariable binomial logistic regression analysis for predictors of contracting COVID-19 in the MS population of the UK MS Register MS and COVID-19 study.

	Included in the analysis n	**OR**	**Lower 95% CI**	**Upper 95% CI**	**Adjustments**
Age (1-year increment)	7,971	0.972	0.967	0.977	None
Men vs women	7,977	0.857	0.734	0.999	None
All other ethnicities vs White ethnicity	7,977	1.64	1.244	2.162	None
MS disease duration (1-year increment)	7,781	1.01	1.001	1.019	Age
WebEDSS score [a]	4,408	-	-	-	Age, Gender, Taking a DMT
0–2.5 (reference)	-	1	1	1	
3–3.5	-	0.933	0.713	1.22	
4–5.5	-	1.195	0.947	1.508	
6–6.5	-	0.73	0.573	0.93	
≥ 7	-	0.854	0.631	1.133	
MS type	7,781	-	-	-	Age, Gender, MS disease duration
RRMS (reference)	-	1	1	1	
SPMS	-	0.729	0.599	0.887	
PPMS	-	0.681	0.514	0.903	
Taking a DMT	7,970	0.85	0.731	0.989	Age, MS type

95% CI = 95% Confidence Interval; DMT = Disease-Modifying Therapy; OR = Odds Ratio; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

2.4. Discussion

We report initial findings of an ongoing community-based COVID-19 study in a large UK-wide population of people with MS which coincided with the peak of the COVID-19 outbreak in the UK.[4] We show that people with MS taking immunomodulatory treatments do not have an increased risk of contracting COVID-19. We did not find individual DMTs to be noticeably over-represented among people with MS with COVID-19.

The incidence of COVID-19 in our population of people with MS was not higher than that of the general population,[5] and people with MS were not at a higher risk of having COVID-19 compared with their siblings without MS. The low hospitalisation rate in our population is possibly due to its patient-reported nature where hospitalised people with MS would fail to respond to the surveys.

The observation that self-isolating people with MS had a lower risk of COVID-19 was not unexpected. We found older people with MS and those with PMS were less likely to have COVID-19. This could be because they were self-isolating more. Similar to previous reports, we found evidence that people with MS with any ethnicity other than white had a higher chance of contracting COVID-19,[6] but larger numbers are required to confirm this.

When this study launched, there was no accurate or accessible test to diagnose COVID-19. Therefore, we decided to set a diagnosis of COVID-19 made by participants, based on their symptoms, as the primary outcome of

the study. This approach has also been adopted in other large-scale studies and is in line with the UK government policy not to seek medical advice for mild symptoms of COVID-19.[7 8]

In conclusion, during a period with strict precautions in place to prevent the spread of COVID-19, people with MS and those taking DMTs are not at an increased risk of contracting the disease.

2.4.1. Up-to-date Literature Review

From the start of the COVID-19 pandemic, MS and COVID-19 research mainly covered the severe outcomes of infection in this population, such as hospitalisation (including intensive care unit admission) and death, and their risk factors.[9] A national German study reported that the risk of COVID-19 related severe outcomes in hospitalised people with MS is similar to that of hospitalised people without MS.[10] Other studies—conducted prior to the introduction of COVID-19 vaccines, consistently showed that physical disability is a risk factor for severe COVID-19 outcomes within the MS population.[9 11-13] Some studies suggested that treatment with anti-CD20 agents (i.e., ocrelizumab and rituximab at the time of these studies) and recent corticosteroid use increased the risk of severe COVID-19 in this population.[9 13 14] Other risk factors for severe COVID-19 in people with MS included old age, male sex, obesity, and comorbidities (including cardiovascular disease, pulmonary disease, hypertension, and diabetes mellitus), which were common with the general population.[9] I was involved in

a study (not included in this thesis) of the UK MS Register that reported clinical outcomes of COVID-19 in people with MS and showed similar findings.[15]

This chapter, however, focuses on the risk of contracting COVID-19 in people with MS. The updated results until 19th March 2021—when social restrictions were still in place, corroborate the initial findings of the study. The larger study population of the extended analysis allowed for estimating the risk of contracting COVID-19 associated with individual DMTs; none of the DMTs were found to increase this risk. An Italian MS registry study covering the same period, however, showed that people with MS receiving natalizumab, who required frequent hospital-based administration of their DMT, were at higher risk of contracting COVID-19.[16] This discrepancy between the findings of the UK and Italian MS registry studies can be due to different COVID-19 safety rules and procedures in place within the communities and health care settings. The Italian study also found that younger age, female sex, and comorbidities increased the risk of contracting COVID-19—probably because younger people were more socially active and people with comorbidities often visited health care settings.[16] These findings were in line with the updated results of the UK MS Register study.

2.5. References

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Chapter 3

COVID-19 Is Associated with MS Exacerbations

3. COVID-19 Is Associated with MS Exacerbations

The published article[1] is included in Appendix 3-A.

3.1. Abstract

3.1.1. Background

Infections can trigger exacerbations of MS. The effects of COVID-19 on MS are unknown. The aim of this study was to understand the impact of COVID-19 on new and pre-existing symptoms of MS.

3.1.2. Methods

The COVID-19 and MS study is an ongoing community-based, prospective cohort study conducted as part of the UKMSR. People with MS and COVID-19 were invited by email to complete a questionnaire about their MS symptoms during the infection. An MS exacerbation was defined as developing new MS symptoms and/or worsening of pre-existing MS symptoms.

3.1.3. Results

Fifty-seven percent (n = 230 out of 404) of participants had an MS exacerbation during their infection; 82 developed new MS symptoms, 207 experienced worsened pre-existing MS symptoms, and 59 reported both. DMTs reduced the likelihood of developing new MS symptoms during the infection (OR: 0.556, 95% CI: 0.316–0.978). Participants with a higher pre-COVID-19 webEDSS score (OR: 1.251, 95% CI: 1.060–1.478) and longer MS

duration (OR: 1.042, 95% CI: 1.009–1.076) were more likely to experience worsening of their pre-existing MS symptoms during the infection.

3.1.4. Conclusion

COVID-19 was associated with exacerbation of MS. DMTs reduced the chance of developing new MS symptoms during the infection.

3.2. Introduction

The role of systemic infections in provoking exacerbations of MS is well described.[2-4] COVID-19 is a viral infection, the effects of which on MS exacerbations have not been established. Understanding the impact of COVID-19 on MS symptoms will allow for thorough counselling of people with MS regarding the risk of infection during periods of community transmission.

Potential safety concerns about using immunosuppressive MS DMTs during the COVID-19 pandemic,[5] along with disruptions to MS services,[6] resulted in changes to the treatment plans of many people with MS.[7] However, a decrease in the use of DMTs during the pandemic could lead to excessive MS relapses. Further understanding of the relationship between COVID-19, MS relapses and DMTs will inform decision-making about altering or delaying treatment with DMTs.

In this paper, we study the impact of COVID-19 on pre-existing and new symptoms of MS in a large cohort of people with MS and COVID-19. We also assess potential factors associated with COVID-19-related MS exacerbations.

3.3. Materials and Methods

The COVID-19 and MS study was an ongoing national community-based, prospective cohort study conducted as part of the UKMSR. People with MS reported whether they had symptoms consistent with COVID-19, whether the diagnosis was confirmed by a healthcare provider based on their clinical or laboratory findings, and whether they had been admitted to a hospital because of their infection.

People with MS and symptoms consistent with COVID-19 were invited to complete a questionnaire about their MS symptoms during or soon after the infection, between 20th July 2020 and 25th January 2021. We asked participants about any new or worsened pre-existing MS symptoms (Appendix 3-B). Here, we report our cross-sectional findings according to the STROBE guidelines.[8]

We defined an MS exacerbation as developing new MS symptoms, worsening of pre-existing MS symptoms, or experiencing both during a COVID-19 infection. We asked participants about limitation in daily activities caused by the new symptoms and classified them as mild (no limitation), moderate (less than 50% limitation), or severe (more than 50% limitation).

We correlated the COVID-19 and MS symptoms data with information held by the UKMSR on participants' demographics (age, sex, and ethnicity), clinical characteristics (MS type, disease duration from diagnosis, and DMTs), most recent recorded webEDSS scores (scored 0–10, with higher scores indicating

more neurological impairment) from before their infection,[9] and most recent Hospital Anxiety and Depression Scale (HADS) scores (scored 0–21, with scores ≥11 considered as probable cases of anxiety or depression).[10]

3.3.1. Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA; 2019).

Continuous data were compared using the independent samples *t* test, if normally distributed (mean [SD]) or the Mann-Whitney *U* test, when not normally distributed (also used for comparing ordinal variables; median [IQR]). Categorical variables were analysed using the $\chi 2$ (Chi-square) test (or the Fisher exact test if expected count ≤5). For variables with missing data, the number of valid values is stated.

The association between different dependent (developing new MS symptoms, worsening of pre-existing MS symptoms) and independent variables (age, sex, type of MS, MS disease duration, pre-COVID-19 webEDSS score, DMT use) was assessed using univariable or multivariable binomial logistic regression analysis. To avoid introducing bias by controlling for colliders and mediators in the regression analyses models, DAGs were built to determine confounding factors for individual regression analyses (Appendix 3-C).[11 12] Confounding factors controlled for in each analysis have been stated. Listwise deletion was implemented for missing data. The results of the regression analyses are presented as OR and 95% CI.

3.3.2 Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval for UKMSR studies was obtained from South West-Central Bristol Research Ethics Committee (16/SW/0194). Participants provided informed consent online. The study is registered on clinicaltrials.gov: NCT04354519.

3.3.3. Data Availability Policy

Data are stored on the UKMSR Secure e-Research Platform at Swansea University Medical School. Line level data cannot be released, but qualified researchers, subject to governance, can request access to data.

3.4. Results

We invited 978 people with MS and COVID-19 to complete the MS symptoms questionnaire and 404 (41%) responded within a median (IQR) duration of 14 (9–17) weeks from reporting a diagnosis of COVID-19 (Table 3.1).

Table 3.1. Demographic and clinical characteristics of participants and non-participants.

	Participants n = 404	**Non-participants** n = 574	***p* value**
Age mean (SD), years	50 (11)	48 (11)	0.001
Women n (%)	307 (76)	456 (79.4)	0.434
White ethnicity n (%)	380 (94.1)	538 (93.7)	0.832
WebEDSS score [a] median (IQR)	4.5 (3–6.5) n = 248	4 (3–6.5) n = 288	0.776

	Participants n = 404	Non-participants n = 574	*p* value
MS type n (%)			
RRMS	277 (68.6)	415 (72.3)	0.018
SPMS	65 (16.1)	99 (17.2)	
PPMS	39 (9.7)	26 (4.5)	
Unknown	23 (5.7)	34 (5.9)	
MS disease duration median (IQR), years	11 (5–18) n = 395	10 (5–17) n = 547	0.106
DMTs n (%)	193 (47.8)	301 (52.4)	0.151
Beta-interferons	21 (5.2)	39 (6.8)	
Glatiramer acetate	22 (5.4)	37 (6.5)	
Teriflunomide	7 (1.7)	14 (2.4)	
Dimethyl fumarate	58 (14.4)	72 (12.6)	
Fingolimod	24 (5.9)	35 (6.1)	
Siponimod	0 (0)	1 (0.2)	
Natalizumab	24 (5.9)	44 (7.7)	
Ocrelizumab	14 (3.5)	33 (5.8)	
Cladribine	7 (1.7)	9 (1.6)	
Alemtuzumab	13 (3.2)	15 (2.6)	
Others [b]	3 (0.7)	1 (0.2)	
Confirmed COVID-19 n (%)	108 (26.7)	168 (29.3)	0.386
Hospitalised due to COVID-19 n (%)	8 (2)	9 (1.6)	0.620

DMTs = Disease-Modifying Therapies; IQR = Interquartile Range; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SD = Standard Deviation; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] The median (IQR) duration from recording the webEDSS score to reporting COVID-19 was 7 (3–16.75) weeks for participants and 11 (6–23.75) weeks for non-participants (p <0.001). WebEDSS score were recorded prior to COVID-19 onset.

[b] Participants were taking Ponesimod (n = 1) and Rituximab (n = 2), and the non-participant was taking Azathioprine.

Two hundred and thirty (57%) participants had an MS exacerbation, with 82 (20%) developing new symptoms, 207 (51%) experiencing worsened pre-existing symptoms, and 59 (15%) reporting both during their COVID-19 infection.

Ninety-seven percent (n = 222) of participants with an MS exacerbation (80 with new MS symptoms and 199 with worsened pre-exiting MS symptoms) had fever during their infection compared to 68% (n = 72) of participants without an MS exacerbation (p <0.001). Six (3%) participants with an MS exacerbation (2 with new MS symptoms and all 6 with worsened pre-existing MS symptoms) and 2 (1%) participants without an MS exacerbation were hospitalised due to COVID-19 (p = 0.296).

The rate of MS exacerbations was not significantly different between participants with (n = 108) and without (n = 296) a confirmed diagnosis of COVID-19 (63.9% versus 54.4%, p = 0.088).

A higher proportion of participants with anxiety and/or depression reported an MS exacerbation during their infection compared to participants without anxiety or depression (68% [78/114] versus 51% [109/212], p = 0.003), with 32% (n = 36) and 14% (n = 30) reporting new MS symptoms, respectively, and 61% (n = 69) and 48% (n = 101) reporting worsened pre-existing MS symptoms, respectively.

Thirty-nine percent (77/196) of the participants with an MS exacerbation required additional support for their daily activities during COVID-19 infection, as opposed to only 6% (7/114) of the participants without an exacerbation (p <0.001).

3.4.1. New MS Symptoms

Among the 82 participants with new MS symptoms during the infection, the most reported new symptoms were sensory, motor, or both (n = 58; 71%) (Table 3.2). Some COVID-19 symptoms such as fatigue, memory problems, or mobility problems can mimic MS symptoms. Most participant who reported fatigue (n = 18), memory problems (n = 17), or mobility problems (n = 24) as part of their new MS symptoms during the infection had additional non-COVID-19-related neurological symptoms including sensory, motor, visual, or balance problems (89%, 88%, and 71%, respectively).

Table 3.2. Reported new MS symptoms during COVID-19.

Symptoms [a] n = 82	**n (%)**
Weakness	27 (6.7)
Mild	6 (22.2)
Moderate	14 (51.9)
Severe	7 (25.9)
Sensory symptoms (numbness, pins and needles, or pain)	43 (10.6)
Mild	12 (30.8)
Moderate	24 (61.5)
Severe	7 (17.9)

Symptoms [a] n = 82	**n (%)**
Balance problems	24 (5.9)
Mild	5 (20.8)
Moderate	14 (58.3)
Severe	5 (20.8)
Bladder or bowel problems	15 (3.7)
Mild	4 (28.6)
Moderate	6 (42.9)
Severe	5 (35.7)
Visual problems (blurred vision or double vision)	12 (3)
Mild	5 (41.7)
Moderate	3 (25)
Severe	4 (33.3)
Fatigue	18 (4.5)
Mild	3 (16.7)
Moderate	6 (33.3)
Severe	9 (50)
Memory problems	17 (4.2)
Mild	3 (17.6)
Moderate	9 (52.9)
Severe	5 (29.4)
Mobility problems	24 (5.9)
Mild	3 (12.5)
Moderate	13 (54.2)
Severe	8 (33.3)
Others [b]	10 (2.5)

[a] Symptoms causing no limitation in daily activities were considered as mild, symptoms causing less than 50% limitation in daily activities as moderate, and symptoms causing more than 50% limitation in daily activities as severe.

[b] Other new MS symptoms included spasms, speech or swallowing difficulties, tremor, or vertigo

Sixteen (20%) participants with new MS symptoms during their infection had mild, 40 (49%) had moderate, and 26 (32%) had severe symptoms. None were treated with steroids.

Taking DMTs reduced the likelihood of developing new MS symptoms during the infection (OR: 0.556, 95% CI: 0.316–0.978, adjusted for type of MS) (Table 3.3). The results were similar after adjusting for age, sex, pre-COVID-19 webEDSS score and type of MS (OR: 0.430, 95% CI: 0.198–0.931). We did not formally test the association between individual DMTs and developing new MS symptoms due to the small number of participants on individual DMTs; however, it seemed that a higher proportion of participants without new MS symptoms during their infection were taking fingolimod, ocrelizumab, or cladribine compared to participants who developed new symptoms (Table 3.4).

Thirty-six (44%) participants with new MS symptoms reported recovery from these symptoms; 21 (26%) recovered within three weeks. Among the 46 participants who had not reported recovery, the median (IQR) duration from reporting COVID-19 to reporting persistence of the symptoms was 14 (10–17) weeks.

Table 3.3. Factors associated with changes in MS symptoms during COVID-19.

	Multivariable regression analysis				Univariable regression analysis		
	OR	**95% CI**	**n [a]**	**Adjustments**	**OR**	**95% CI**	**n [a]**
Developing new MS symptoms (n = 82) **compared to no new MS symptoms** (n = 322)							
Age 1-year increment	No adjustment was required.				0.997	0.975 – 1.019	404
Male vs female	No adjustment was required.				0.550	0.289 – 1.048	403
PMS vs RRMS	1.532	0.814 – 2.883	395	Age, Sex, MS disease duration	1.337	0.779 – 2.296	404
MS disease duration 1-year increment	1.024	0.991 – 1.059	395	Age	1.017	0.989 – 1.046	395
WebEDSS score 1-point increment	1.108	0.929 – 1.322	248	Age, Sex, Type of MS, Taking DMTs	1.059	0.914 – 1.226	248
Taking DMTs	**0.556**	**0.316 – 0.978**	404	Type of MS	0.563	0.341 – 0.928	404
Worsening of pre-existing MS symptoms (n = 207) **compared to no worsening** (n = 128) [b]							
Age 1-year increment	No adjustment was required.				1.016	0.995 – 1.037	335
Male vs female	No adjustment was required.				0.640	0.381 – 1.077	335

	Multivariable regression analysis				Univariable regression analysis		
	OR	**95% CI**	**n [a]**	**Adjustments**	**OR**	**95% CI**	**n [a]**
PMS vs RRMS	1.147	0.625 – 2.106	327	Age, Sex, MS disease duration	1.328	0.786 – 2.243	335
MS disease duration 1-year increment	**1.042**	**1.009 – 1.076**	327	Age	1.044	1.015 – 1.074	327
WebEDSS score 1-point increment	**1.251**	**1.060 – 1.478**	208	Age, Sex, Type of MS, Taking DMT	1.163	1.017 – 1.330	208
Taking DMTs	1.186	0.716 – 1.966	335	Type of MS	1.047	0.673 – 1.627	335

95% CI = 95% Confidence Interval; DMTs = Disease-Modifying Therapies; OR = Odds Ratio; PMS = Progressive MS, which includes primary and secondary progressive MS; RRMS = Relapsing-Remitting MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] Number of participants included in the analysis after listwise deletion of missing data.

[b] Sixty-nine participants did not recall whether their pre-existing MS symptoms had become worse or not during their COVID-19.

Table 3.4. Characteristics of participants with and without new symptoms of MS during COVID-19.

	With new MS symptoms n = 82	**Without new MS symptoms** n = 322	***p* value**
Age mean (SD), years	50 (11)	50 (11)	0.784
Female n (%)	68 (82.9)	239 (74.2)	0.066
White ethnicity n (%)	79 (96.3)	301 (93.5)	0.327

	With new MS symptoms n = 82	Without new MS symptoms n = 322	*p* value
WebEDSS score median (IQR)	5 (2.875–6.5) n = 50	4 (3–6.5) n = 198	0.481
MS type n (%)			
RRMS	53 (64.6)	224 (69.6)	0.589 [a]
SPMS	14 (17.1)	51 (15.8)	
PPMS	11 (13.4)	28 (8.7)	
Unknown	4 (4.9)	19 (5.9)	
MS disease duration median (IQR), years	11.5 (5–20.5) n = 80	11 (6–17) n = 315	0.564
DMTs [b] n (%)	30 (36.6)	163 (50.6)	0.023
Beta-interferons	4 (13.3)	17 (10.4)	
Glatiramer acetate	6 (20)	16 (9.8)	
Teriflunomide	2 (6.7)	5 (3.1)	
Dimethyl fumarate	8 (26.7)	50 (30.7)	
Fingolimod	2 (6.7)	22 (13.5)	
Natalizumab	5 (16.7)	19 (11.7)	
Ocrelizumab	1 (3.3)	13 (8)	
Cladribine	0 (0)	7 (4.3)	
Alemtuzumab	2 (6.7)	11 (6.7)	
Others [c]	0 (0)	3 (1.8)	
Required more help [d] n (%)	28 (39.4)	68 (23.9)	0.009

DMTs = Disease-Modifying Therapies; IQR = Interquartile Range; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = web-based Expanded Disability Status Scale

[a] One cell (12.5%) has expected count less than 5.

[b] Percentages of individual DMTs are calculated based on the total number of participants taking DMTs in each group.

[c] Participants were taking Ponesimod (n = 1) and Rituximab (n = 2).

[d] During their COVID-19 compared to before.

3.4.2. Pre-existing MS Symptoms

Among the 207 participants with worsened pre-existing MS symptoms during the infection (Table 3.5), 190 (92%) reported this worsening to be the same as (n = 91) or worse than (n = 99) their previous non-COVID-19 systemic infection.

Table 3.5. Characteristics of participants with and without worsened pre-existing MS symptoms during COVID-19.

	With worsened pre-existing MS symptoms n = 207	**Without worsened pre-existing MS symptoms** n = 128 [a]	***p* value**
Age mean (SD), years	51 (11)	49 (11)	0.140
Female n (%)	166 (80.2)	93 (72.7)	0.176
White ethnicity n (%)	197 (95.2)	117 (91.4)	0.167
WebEDSS score median (IQR)	4.5 (3–6.5) n = 133	4 (2.5–6.5) n = 75	0.035
MS type n (%)			
RRMS	138 (66.7)	90 (70.3)	0.648
SPMS	36 (17.4)	18 (14.1)	
PPMS	21 (10.1)	10 (7.8)	
Unknown	12 (5.8)	10 (7.8)	
MS disease duration median (IQR), years	12 (7–19) n = 203	8 (4–15.75) n = 124	0.001

	With worsened pre-existing MS symptoms n = 207	Without worsened pre-existing MS symptoms n = 128 [a]	*p* value
DMTs [b] n (%)	101 (48.8)	61 (47.7)	0.840
Beta-interferons	9 (8.9)	9 (14.8)	
Glatiramer acetate	11 (10.9)	6 (9.8)	
Teriflunomide	3 (3)	1 (1.6)	
Dimethyl fumarate	36 (35.6)	14 (23)	
Fingolimod	13 (12.9)	9 (14.8)	
Natalizumab	13 (12.9)	8 (13.1)	
Ocrelizumab	6 (5.9)	5 (8.2)	
Cladribine	3 (3)	4 (6.6)	
Alemtuzumab	5 (5)	5 (8.2)	
Others [c]	2 (1.2)	0 (0)	
Required more help [d] n (%)	70 (39.8)	8 (6.6)	<0.001

DMTs = Disease-Modifying Therapies; IQR = Interquartile Range; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] Sixty-nine participants did not recall whether their pre-existing MS symptoms had become worse or not during their COVID-19 infection.

[b] Percentages of individual DMTs are calculated based on the total number of participants taking DMTs in each group.

[c] Participants were taking Ponesimod (n = 1) and Rituximab (n = 1).

[d] During their COVID-19 compared to before.

The pre-existing MS symptoms of participants with a higher pre-COVID-19 webEDSS score (OR: 1.251, 95% CI: 1.060–1.478) and longer MS disease duration (OR: 1.042, 95% CI: 1.009–1.076) were more likely to worsen during the infection (Table 3.3).

Sixty-three (30%) participants who experienced worsening of their pre-existing MS symptoms during the infection reported returning to baseline; 42 (20%) recovered within three weeks. Among the 144 participants who had not returned to baseline, the median (IQR) duration from reporting COVID-19 to responding to the questionnaire was 14 (9–16) weeks.

3.5. Discussion

This large community-based study found that 57% of people with MS and COVID-19 experience an MS exacerbation during their infection, including 20% who develop new MS symptoms. Previous studies have demonstrated an increased risk of MS exacerbations associated with other infections,[2] but the rates (9–41%) are lower than COVID-19-related exacerbations reported in this study.[13-17] This difference could suggest a difference between COVID-19 and other common systemic infections in inducing MS exacerbations; however, it should be noted that our findings could have been influenced by recall bias. We could not objectively assess the reported new MS symptoms by neurological examination to confirm that they were relapses due to the restrictions caused by the pandemic. Previously, it has been shown that relapses reported by people with MS are often also diagnosed as relapses by clinicians.[18] Our study did not include a control group of people with MS without COVID-19 and therefore, we could not assess the absolute risk of MS exacerbations associated with COVID-19.

An association between DMT use and reduction of infection-related exacerbations of MS has not been conclusively established.[13 16] We found that taking a DMT reduces the probability of developing new MS symptoms during COVID-19 infection by 44%, which is consistent with the overall relapse rate reduction, in the absence of infection, observed in clinical trials of current DMTs.[19] Our data suggest that different DMTs might have a variable effect in preventing COVID-19-related new MS symptoms. This very preliminary finding is interesting but needs to be confirmed in larger case-control studies to (1) provide a precise estimation of the association between DMT use and infection-related relapses, and (2) compare this association to the effectiveness of DMTs in preventing non-infection-related relapses.

Studies have suggested that infection-related exacerbations can be more severe and prolonged compared to exacerbations not induced by an infection.[13 14] In our study, the MS exacerbation of many participants had not resolved three months after their COVID-19. Most individuals with COVID-19-related worsening of their MS symptoms reported a deterioration that was worse than or similar to their previous non-COVID-19 infection. This finding could have been influenced by recall bias, however. In addition, most individuals reported that their new MS symptoms resulted in limitation of their daily activities.

We wondered whether people had regarded their COVID-19 symptoms, such as fatigue or cognitive problems that can mimic MS symptoms, as deterioration of their MS. Can we truly distinguish MS deterioration from

some systemic symptoms of COVID-19? We cannot answer this question with confidence without paraclinical tests, but we found that most individuals with fatigue, memory, or mobility problems also reported other neurological symptoms suggestive of MS.

Although more individuals with anxiety or depression reported an MS exacerbation during their COVID-19 than individuals without anxiety or depression, the rate of MS exacerbations was above 50% in both groups, suggesting that over-reporting of symptoms linked to anxiety or depression has not driven these results.[20]

3.5.1. Up-to-date Literature Review

Following the publication of this article, a few smaller studies also examined the effect of COVID-19 on the course of MS. An Austrian MS-COVID-19 registry (AUT-MuSC) study did not find an association between COVID-19 and MS relapses or disability progression.[21] Participants of this study were followed up for 12 months and 75% of them were receiving a DMT, with 39% receiving a high-efficacy DMT.[21] An Italian clinic-based study could not show any relationship between COVID-19 and MS relapses, disability progression, or radiological disease activity in their 6 month follow-up.[22] All the population of this study received a DMT, with 65% receiving a high-efficacy DMT.[22] The MS outcome in both these studies, however, was the occurrence of an MS relapse (i.e., in the absence of fever or infection), and not an infection-related MS exacerbation,[21 22] as opposed to the UKMSR study. The UKMSR study

included a higher proportion of untreated people with MS with only 48% of the study population receiving a DMT and 21% receiving a high-efficacy DMT. The higher rate of DMT use in the former studies could have contributed to the low rate of MS relapses following COVID-19, in line with the findings of the UKMSR study.[21 22] A single centre Belgian study, showed that 24% of people with MS and COVID-19 (n = 138 people with MS who survived COVID-19) experience clinically relevant disability progression following COVID-19 (as assessed by their EDSS scores) compared to only 12% in a same period before contracting COVID-19.[23] However, the scores of the study population on the timed 25-feet walk test, the 9-hole peg test, and the symbol digit modalities test had not significantly changed following COVID-19.[23]

3.5.2. Conclusion

These findings indicate that although COVID-19 can cause MS exacerbations, it does not necessarily alter the course of MS in terms of clinical or radiological disease activity. These MS exacerbations may, however, have a negative impact on other aspects of the lives of people with MS (e.g., quality of life, employment, physical activity, etc.) with long-term implications, which have not been studied. DMTs seem to protect people with MS against infection-related as well as true MS relapses following COVID-19. Therefore, decisions around the choice of DMT, when considering the risk of infection, should be based on a thorough risk-benefit assessment. These findings also highlight the importance of preventing infection in the MS population by offering COVID-19 vaccines and advocating the vaccination programmes.

3.6. References

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Chapter 4

Recovery From COVID-19 in MS

4. Recovery From COVID-19 in MS

A Prospective and Longitudinal Cohort Study of the UK MS Register

The published article[1] is included in Appendix 4-A.

4.1. Abstract

4.1.1. Objectives

To understand the course of recovery from COVID-19 among people with MS, and to determine its predictors, including patients' pre-COVID-19 physical and mental health status.

4.1.2. Methods

This prospective and longitudinal cohort study recruited people with MS who reported COVID-19 from 17th March 2020 to 19th March 2021 as part of the UKMSR COVID-19 study. Participants used online questionnaires to regularly update their COVID-19 symptoms, recovery status, and duration of symptoms for those who fully recovered. Questionnaires were date-stamped for estimation of COVID-19 symptom duration for those who had not recovered at their last follow-up. The UKMSR holds demographic and up-to-date clinical data on participants as well as their webEDSS and HADS scores. The association between these factors and recovery from COVID-19 was assessed using multivariable Cox regression analysis.

4.1.3. Results

Of the 7,977 people with MS who participated in the UKMSR COVID-19 study, 599 reported COVID-19 and prospectively updated their recovery status. Twenty-eight hospitalised participants were excluded. At least 165 participants (29.7%) had long-standing COVID-19 symptoms for ≥4 weeks and 69 (12.4%) for ≥12 weeks. Participants with pre-COVID-19 webEDSS scores ≥7, participants with probable anxiety and/or depression (HADS scores ≥11) before COVID-19 onset, and women were less likely to report recovery from COVID-19.

4.1.4. Discussion

People with MS are affected by post-acute sequelae of COVID-19. Pre-existing severe neurologic impairment or mental health problems appear to increase this risk. These findings can have implications in tailoring their post-COVID-19 rehabilitation.

4.2. Introduction

Many people with MS evade the serious acute complications of COVID-19, such as hospitalisation, respiratory failure, or death.[2 3] Nevertheless, they may still have long-term effects of the infection, known as post-acute sequelae of COVID-19.

Understanding the burden of post-acute sequelae of COVID-19 among people with MS and identifying its risk factors will inform MS rehabilitation services,

which are going to deal with the emerging needs of people with MS who had COVID-19. In this study, we aim to understand the course of recovery from COVID-19 in MS and to determine its predictors.

4.3. Methods

4.3.1. Study Population and Outcome Measures

This prospective and longitudinal cohort study was conducted as part of the UKMSR COVID-19 study.[3] People with MS had been reporting whether they had symptoms suggestive of COVID-19 and whether their diagnosis was confirmed by a health care provider or COVID-19 testing, from 17th March 2020—the start of the outbreak in the UK.[3] Further information about COVID-19 testing was not collected, but, in the UK, people with COVID-19 symptoms are only offered an RT-PCR test. Mass COVID-19 testing in the UK was implemented on 28th May 2020—before then, PCR tests were only available to inpatients. All data were collected using online questionnaires.

People with MS with self-reported symptoms suggestive of COVID-19 were included in the study. They were followed up, by email reminders, every two weeks to update their COVID-19 symptoms and recovery status until reporting full recovery from COVID-19 symptoms (questions provided in Appendix 4-B). Participants who reported full recovery also provided the duration of their COVID-19 symptoms. The submitted questionnaires were date-stamped for estimation of COVID-19 symptom duration for participants

who had not reported full recovery at their last follow-up. Participants were asked to specifically report new or worsened symptoms after their COVID-19.

The UKMSR holds demographic and up-to-date clinical data on registered people with MS, including comorbidities, MS type, date of MS diagnosis, DMTs, webEDSS scores, and HADS scores. The most recent webEDSS and HADS scores before COVID-19 onset were used.

Participants were grouped into five groups based on their webEDSS score: (1) 0–2.5 (ambulatory without assistance and no or minimal neurologic impairment), (2) 3–3.5 (ambulatory without assistance and moderate neurologic impairment), (3) 4–5.5 (ambulatory without assistance and severe neurologic impairment), (4) 6–6.5 (ambulatory with assistance), and (5) ≥7 (restricted to wheelchair or bed).[4]

HADS is scored (0–21) for anxiety and depression separately. Participants with HADS scores of ≥11 were considered as having probable anxiety or depression.[5] Participants with anxiety, depression, or both were considered as one group because these conditions frequently co-exist in MS,[6] and the number of participants with anxiety or depression alone was small.

Data collected until 19th March 2021 are presented according to STROBE guidelines.[7]

4.3.2. Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval for UKMSR studies was obtained from Southwest-Central Bristol Research Ethics Committee (16/SW/0194). All participant provided informed consent online. The study is registered with ClinicalTrials.gov: NCT04354519.

4.3.3. Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA; 2019).

Continuous variables with normal distribution are presented as mean (SD) and were compared using the independent samples *t* test. Continuous variables without normal distribution and ordinal variables are presented as median (IQR) and were compared using the Mann-Whitney *U* test. The association between categorical variables was assessed using the χ^2 (Chi-square) test or the Fisher exact test. The number of valid values for variables with missing data has been stated.

Univariable and multivariable Cox regression analysis, with time (days) from reporting COVID-19 to full recovery (event) as the dependent variable, were performed to assess the association between demographic and clinical variables and recovery from COVID-19. Participants with persistent symptoms at their last follow-up were censored. A DAG was produced (Appendix 4-C) to identify potential confounding factors, which were subsequently accounted for in the multivariable Cox regression analysis. This method avoids the

introduction of bias in the analysis by the erroneous inclusion of colliders and mediators as confounding factors.[8] Listwise deletion was implemented for missing data. Results are presented as adjusted hazard ratios with 95% CIs.

4.3.4. Data Availability

Data are stored on the UKMSR Secure e-Research Platform at Swansea University Medical School. Line level data cannot be released, but qualified researchers- subject to governance, can request access to data.

4.4. Results

Of the 7,977 people with MS who participated in the UKMSR COVID-19 study, 1,096 reported COVID-19. A total of 599 people with MS and COVID-19 updated their recovery status (participants) and 497 did not (nonparticipants). Twenty-eight participants (4.7%) and 8 (1.6%) nonparticipants were hospitalised during their acute infection ($p = 0.05$). Only 16 participants (and all hospitalised nonparticipants) were admitted to hospital because of COVID-19. Therefore, hospitalised people with MS were excluded from the analysis. Participants did not differ in their baseline characteristics (including demographics, MS type, webEDSS score, DMTs, comorbidities, or having anxiety and/or depression) from nonparticipants, except for a lower rate of hypertension among participants (10.8%) than non-participants (16.3%) (Table 4.1).

Table 4.1. Characteristics of people with MS with COVID-19 who updated (participants) or did not update (nonparticipants) their recovery status.

	Participants n = 571	**Participants with confirmed COVID-19** [a] n = 187	**Nonparticipants** n = 489	***p* value** [b]
Age mean (SD), years	49 (11)	48 (11)	48 (11)	0.254
Women no (%)	441 (77.2)	145 (77.5)	390 (79.8)	0.260
White ethnicity no (%)	541 (94.7)	178 (95.2)	454 (92.8)	0.198
Comorbidities [c] no (%)				
Diabetes	17 (3.8) n = 443	4 (2.9) n = 136	8 (2.4) n = 332	0.266
Heart disease	8 (1.8) n = 443	2 (1.5) n = 136	5 (1.5) n = 332	0.748
Hyperlipidemia	30 (6.8) n = 443	8 (5.9) n = 136	23 (6.9) n = 332	0.932
Hypertension	48 (10.8) n = 443	10 (7.4) n = 136	54 (16.3) n = 332	0.027
Peripheral vascular disease	1 (0.2) n = 443	0 (0) n = 136	0 (0) n = 332	-
Kidney disease	7 (1.6) n = 443	2 (1.5) n = 136	5 (1.5) n = 332	0.934
Liver disease	1 (0.2) n = 443	0 (0) n = 136	2 (0.6) n = 332	-
Lung disease	51 (11.5) n = 443	11 (8.1) n = 136	53 (16) n = 332	0.072
Anxiety and/or Depression [d]	147 (38.1) n = 386	47 (33.8) n = 139	118 (37.2) n = 317	0.815
WebEDSS score [c] median (IQR)	4 (3–6.5) n = 397	4 (3–6.5) n = 147	4 (3–6.5) n = 288	0.872

	Participants n = 571	Participants with confirmed COVID-19 [a] n = 187	Nonparticipants n = 489	*p* value [b]
WebEDSS categories no (%)				
0–2.5	92 (23.2)	30 (20.4)	71 (24.7)	0.909
3–3.5	60 (15.1)	25 (17)	40 (13.9)	
4–5.5	106 (26.7)	42 (28.6)	72 (25)	
6–6.5	90 (22.7)	29 (19.7)	72 (25)	
≥ 7	49 (12.3)	21 (14.3)	33 (11.5)	
MS disease duration median (IQR), years	10 (5–18) n = 553	9 (4–15) n = 199	9 (5–16) n = 465	0.117
Type of MS no (%)				
RRMS	406 (71.1)	141 (75.4)	352 (72)	0.409
SPMS	103 (18)	27 (14.4)	77 (15.7)	
PPMS	37 (6.5)	12 (6.4)	29 (5.9)	
Unknown	25 (4.4)	7 (3.7)	31 (6.3)	
Taking a DMT no (%)	287 (50.3)	96 (51.3)	261 (53.4)	0.312
Alemtuzumab	19 (3.3)	6 (3.2)	9 (1.8)	-
Beta interferons	40 (7)	13 (7)	29 (5.9)	
Cladribine	11 (1.9)	3 (1.6)	6 (1.2)	
Dimethyl fumarate	75 (13.1)	21 (11.2)	63 (12.9)	
Fingolimod	35 (6.1)	10 (5.3)	32 (6.6)	
Glatiramer acetate	28 (4.9)	9 (4.8)	40 (8.2)	
Natalizumab	37 (6.5)	14 (7.5)	38 (7.8)	
Ocrelizumab	25 (4.4)	13 (7)	30 (6.1)	
Rituximab	2 (0.7)	1 (0.5)	0 (0)	

	Participants n = 571	Participants with confirmed COVID-19 [a] n = 187	Nonparticipants n = 489	*p* value [b]
Siponimod	1 (0.2)	1 (0.5)	0 (0)	
Teriflunomide	12 (2.1)	5 (2.7)	13 (2.7)	
Other	2 (0.7)	0 (0)	0 (0)	

DMT = Disease-Modifying Therapy; IQR = Interquartile range; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] A diagnosis of COVID-19 confirmed by a health care provider or testing.

[b] Comparisons were made between all participants and non-participants.

[c] Prior to COVID-19 onset.

[d] Patients with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively.

Four hundred forty-four participants (77.8%) reported full recovery from COVID-19 at their last follow-up. Their median (IQR) symptom duration was 10 (6–21) days (n = 441); 70 recovered in ≥4 weeks and 9 in ≥12 weeks. However, 127 participants (22.2%) had persistent symptoms at their last follow-up. They had been followed up for a median (IQR) of 87 (41–185) days (n = 115) with 95 having symptoms for ≥4 weeks and 60 for ≥12 weeks from reporting COVID-19. Therefore, at least 165 participants (29.7%) had lasting COVID-19 symptoms for ≥4 weeks and 69 (12.4%) for ≥12 weeks. The characteristics of participants by their symptom duration are compared in Table 4.2.

Table 4.2. Characteristics of people with MS with COVID-19 in relation to the duration of their COVID-19 symptoms.

	<4 weeks n = 371	**≥4 weeks** [a] n = 165	**≥12 weeks** n = 69
Age mean (SD), years	49 (11)	50 (11)	51 (11)
Women no (%)	275 (74.1)	136 (82.4) *	59 (85.5) *
White ethnicity no (%)	350 (94.3)	157 (95.2)	68 (98.6)
Comorbidities [b] no (%)	n = 295	n = 125	n = 53
Diabetes	12 (4.1)	3 (2.4)	2 (3.8)
Heart disease	6 (2)	1 (0.8)	0 (0)
Hyperlipidemia	21 (7.1)	5 (4)	5 (9.4)
Hypertension	32 (10.8)	13 (10.4)	7 (13.2)
Peripheral vascular disease	1 (0.3)	0 (0)	0 (0)
Kidney disease	3 (1)	3 (2.4)	0 (0)
Liver disease	1 (0.3)	0 (0)	0 (0)
Lung disease	30 (10.2)	18 (14.4)	10 (18.9)
Anxiety and/or depression [c]	80 (31.7) n =252	57 (50.4) ** n = 113	25 (54.3) * n = 46
WebEDSS score [b] median (IQR)	4 (2.625–6.5) n = 264	5 (3–6.5) n = 113	5.5 (4–6.5) * n = 50
WebEDSS categories no (%)			
0–2.5	66 (25)	23 (20.4)	7 (14)
3–3.5	45 (17)	11 (9.7)	4 (8)
4–5.5	69 (26.1)	32 (28.3)	15 (30)
6–6.5	53 (20.1)	31 (27.4)	15 (30)
≥ 7	31 (11.7)	16 (14.2)	9 (18)
MS disease duration median (IQR), years	10 (5–17) n = 359	11 (5.25–19) n = 160	13 (6.25–19) n = 68

	<4 weeks n = 371	≥4 weeks [a] n = 165	≥12 weeks n = 69
Type of MS no (%)			
RRMS	265 (71.4)	114 (69.1)	48 (69.6)
SPMS	65 (17.5)	33 (20)	15 (21.7)
PPMS	24 (6.5)	10 (6.1)	5 (7.2)
Unknown	17 (4.6)	8 (4.8)	1 (1.4)
Taking a DMT no (%)	188 (50.7)	84 (50.9)	32 (46.4)
Alemtuzumab	14 (3.8)	4 (2.4)	2 (2.9)
Beta interferons	31 (8.4)	5 (3)	2 (2.9)
Cladribine	8 (2.2)	3 (1.8)	0 (0)
Dimethyl fumarate	49 (13.2)	25 (15.2)	10 (14.5)
Fingolimod	22 (5.9)	11 (6.7)	3 (4.3)
Glatiramer acetate	16 (4.3)	12 (7.3)	7 (10.1)
Natalizumab	23 (6.2)	10 (6.1)	4 (5.8)
Ocrelizumab	15 (4)	8 (4.8)	3 (4.3)
Rituximab	0 (0)	2 (1.2)	1 (1.4)
Siponimod	1 (0.3)	0 (0)	0 (0)
Teriflunomide	8 (2.2)	3 (1.8)	0 (0)
Other	1 (0.3)	1 (0.6)	0 (0)

DMT = Disease-Modifying Therapy; IQR = Interquartile range; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] Includes participants with COVID-19 symptoms for ≥12 weeks.

[b] Prior to COVID-19 onset.

[c] Participants with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively.

* $p < 0.05$ and ** $p = 0.001$. Comparisons were made to participants with symptom duration of <4 weeks.

A post hoc analysis among participants with a COVID-19 diagnosis confirmed by a health care provider or testing showed similar findings. Three hundred and one participants (52.7%) had reported COVID-19 before 28th May 2022, when they could not have been tested outside of hospital admissions. A total of 187 participants (32.7%) had their diagnosis confirmed by a health care provider or testing. A hundred and thirty participants with confirmed COVID-19 (69.5%) reported full recovery. Their median (IQR) symptom duration was 10 (7–20.5) days (n = 129) with 20 experiencing symptoms for ≥4 weeks and 2 for ≥12 weeks. Participants with confirmed COVID-19 and persistent symptoms at their last follow-up had been followed up for a median (IQR) of 49 (35.5–151.25) days (n = 52) with 41 having lasting symptoms for ≥4 weeks and 19 for ≥12 weeks. As a result, at least 33.7% of participants with confirmed COVID-19 (n = 61) had lasting COVID-19 symptoms for ≥4 weeks and 11.6% (n = 21) for ≥12 weeks.

Participants with a pre-COVID-19 webEDSS score of ≥7, participants with anxiety and/or depression before COVID-19 onset, and women were less likely to report recovery from COVID-19 (Table 4.3).

Table 4.3. Results of the multivariable Cox regression analysis[a] of pre-COVID-19 factors associated with recovery from COVID-19.

	Included in the analysis n	**Censored** n	**aHR**	**Lower 95% CI**	**Upper 95% CI**	**Adjustments**
Age (1-year increment)	556	115	0.996	0.988	1.005	None
Women vs men	556	115	**0.756**	**0.609**	**0.937**	None
All other ethnicities vs White ethnicity	556	115	1.374	0.937	2.016	None
MS disease duration (1-year increment)	538	112	0.995	0.983	1.008	Age
Anxiety and/or depression [b, c]	314	65	**0.708**	**0.533**	**0.941**	Age, Gender, Ethnicity, WebEDSS categories
WebEDSS score [c]	380	74	-	-	-	Age, Gender, MS disease duration, MS type
0–2.5 (reference)	-	-	1	1	1	
3–3.5	-	-	1.123	0.783	1.610	
4–5.5	-	-	0.751	0.542	1.040	
6–6.5	-	-	0.698	0.485	1.006	
≥ 7	-	-	**0.614**	**0.381**	**0.989**	
MS type	538	112	-	-	-	Age, Gender, MS disease duration
RRMS (reference)	-	-	1	1	1	
SPMS	-	-	1.049	0.765	1.438	
PPMS	-	-	1.212	0.798	1.841	

	Included in the analysis n	Censored n	aHR	Lower 95% CI	Upper 95% CI	Adjustments
Taking a DMT	556	115	0.985	0.788	1.232	Age, MS type

aHR = Adjusted Hazard Ratio; 95% CI = 95% Confidence Interval; DMT = Disease-Modifying Therapy; PPMS = Primary Progressive MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; WebEDSS = Web-based Expanded Disability Status Scale

[a] Results of the univariable Cox regression analysis is provided in Appendix 4-D.

[b] Participants with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively.

[c] Prior to COVID-19 onset

Of 95 participants who reported their COVID-19 symptoms at ≥4 weeks, 78 (82.1%) had symptoms that were not typical for MS (symptoms listed in Figure 4.1, except for fatigue and pain). Of 60 participants who reported their symptoms at ≥12 weeks, 50 (83.3%) had non-MS related symptoms.

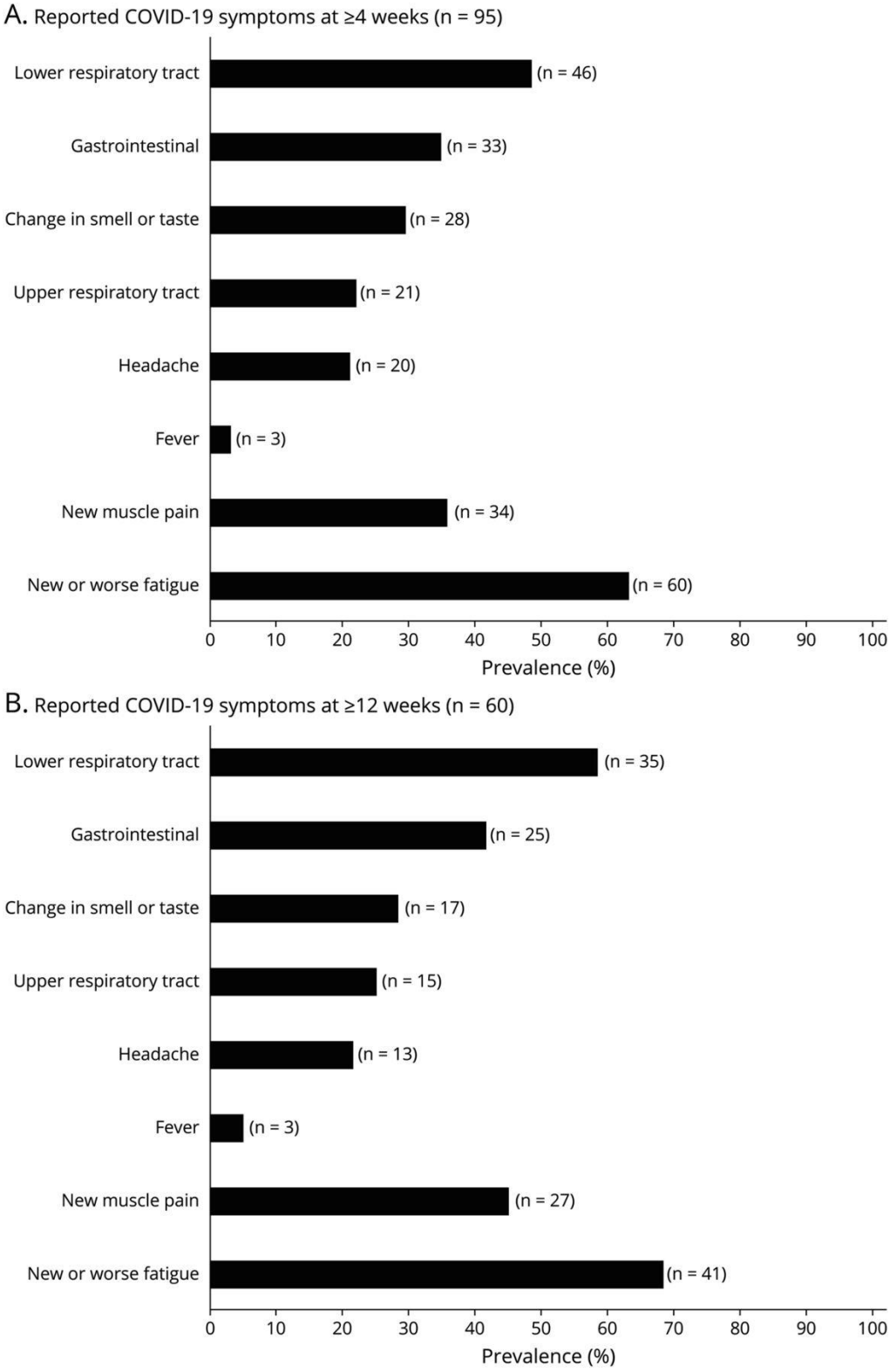

Figure 4.1. Frequency of COVID-19 symptoms among people with MS with persistent symptoms at their last follow-up in ≥4 (A) and ≥12 (B) weeks from reporting COVID-19.
Gastrointestinal symptoms included diarrhoea, nausea or vomiting, or stomach pain. Lower respiratory tract symptoms included coughs, shortness of breath, or heaviness in the chest. Upper respiratory tract symptoms included sore throat, nasal congestion, or sneezing.

4.5. Discussion

This prospective study of a large national cohort of non-hospitalised people with MS and COVID-19 shows that about 30% and 12% of patients experience prolonged COVID-19 symptoms for ≥4 and ≥12 weeks, respectively. These rates in the MS population are higher than the general population, as reported by a study using a similar methodology (13% and 2%, respectively).[9] Another study reports a much higher prevalence of prolonged COVID-19 in the general population, but its retrospective data collection could have led to recall bias.[10] Given that MS shares many neurologic symptoms of COVID-19 and that the infection can lead to MS exacerbations,[11-13] a high prevalence of long-lasting COVID-19 symptoms in this population may seem expected. More than 80% of people with MS with persistent COVID-19 symptoms in the study, however, also had symptoms that were not typical for MS. Further studies using direct control groups, from both the general population and people with MS without COVID-19, are needed to establish the risk of post-acute sequelae of COVID-19 in MS.

An association between physical disability and adverse acute COVID-19 outcomes in MS has been previously reported.[2 14] This study shows that higher levels of pre-COVID-19 neurologic disability predispose people with MS to long-term sequelae of COVID-19 as well. Other MS-related factors such as disease duration or DMTs did not appear to influence recovery from COVID-19. People with MS with pre-COVID-19 mental health problems can also be disproportionately affected by post-acute sequelae of COVID-19,

which has also recently been reported in the general population.[15] The observation that women are more likely to experience prolonged COVID-19 symptoms is in accordance with other studies.[9 16]

4.5.1. Up-to-Date Literature Review

Following the publication of this article, an Austrian MS-COVID-19 registry study (AUT-MuSC) on 211 people with MS and confirmed COVID-19 showed that only 70% of this population recovered from COVID-19 within 3 months (versus 98% in the UKMSR study).[17] In this study, a mild presentation of COVID-19 at onset was found to predict full recovery at follow-up.[17] This finding may explain the above discrepancy between the results of the two studies (the AUT-MuSC and the UKMSR); The UKMSR study included self-reported cases of COVID-19 that were possibly milder—and did not require COVID-19 testing, and, therefore, had a faster recovery.

4.5.2. Limitations

A limitation of the study is that the COVID-19 diagnosis of people with MS was confirmed by laboratory testing in only a proportion of participants, as widespread testing was not available in the UK at the time of recruitment. However, the rates of prolonged COVID-19 in the subgroup with confirmed diagnosis and the total study population were similar. Hospitalised people with MS were excluded to avoid the potential confounding effect of hospitalisation on recovery from COVID-19. The association between hospitalisation and COVID-19 recovery could not be assessed because of the

small sample size of hospitalised people with MS and the risk of selection bias towards non-hospitalised patients due to the questionnaire-based nature of the study.

4.5.3. Conclusion

These findings will inform MS and post-COVID-19 rehabilitation services in developing individualised pathways for people with MS, helping to reduce the burden on these health systems in the COVID-19 era. They also highlight the importance of vaccination against COVID-19 in the MS population who appear to be vulnerable to the long-term effects of infection.

4.6. References

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Chapter 5

Mental Health of People with MS During the COVID-19 Outbreak

5. Mental Health of People with MS During the COVID-19 Outbreak A Prospective Cohort and Cross-Sectional Case-Control Study of the UK MS Register

The published article[1] is included in Appendix 5-A.

5.1. Abstract

5.1.1. Background

People with MS have had higher rates of anxiety and depression than the general population before the COVID-19 pandemic, placing them at higher risk of experiencing poor psychological wellbeing during the pandemic.

5.1.2. Objective

To assess mental health and its social/lifestyle determinants in people with MS during the first wave of the outbreak in the UK.

5.1.3. Methods

This is a community-based, prospective longitudinal cohort and cross-sectional case-control online questionnaire study. It includes 2,010 people with MS from the UK MS Register and 380 people without MS.

5.1.4. Results

The Hospital Anxiety and Depression Scale scores of people with MS for anxiety and depression during the outbreak did not change from the previous year. People with MS were more likely to have anxiety (using General Anxiety

Disorder-7) and/or depression (using Patient Health Questionnaire-9) than controls during the outbreak (OR: 2.14, 95% CI: 1.58–2.91). People with MS felt lonelier (OR: 1.37, 95% CI: 1.04–1.80) reported worse social support (OR: 1.90, 95% CI: 1.18–3.07) and reported worsened exercise habits (OR: 1.65, 95% CI: 1.18–2.32) during the outbreak than controls.

5.1.5. Conclusion

Early in the pandemic, people with MS remained at higher risk of experiencing anxiety and depression than the general population. It is important that multidisciplinary teams improve their support for the wellbeing of people with MS, who are vulnerable to the negative effects of the pandemic on their lifestyle and social support.

5.2. Introduction

The COVID-19 pandemic transformed the lives of people in unpredictable ways and posed a risk to their mental wellbeing.[2] Early in the pandemic, the UK general population experienced higher levels of psychological distress compared to the pre-COVID-19 era.[3] Consequently, research on mental health effects of the pandemic across vulnerable groups became a multidisciplinary research priority.[4]

At the start of the outbreak, anecdotal evidence suggested considerable fear of COVID-19 among people with MS because of their long-term physical disabilities and the immunosuppression caused by some DMTs. The assessment of anxiety and depression in people with MS was specifically

warranted because they were known to have higher pre-COVID-19 rates of anxiety and depression than the general population.[5 6] Furthermore, similar to the general population, changes in lifestyle and social factors could influence the mental health of people with MS.[6-9]

Therefore, we aimed to assess the following:

1. Mental health, its lifestyle and social determinants, and its association with general health among people with MS during the outbreak and compare them to people without MS.
2. Levels of anxiety and depression among people with MS before and after the outbreak.

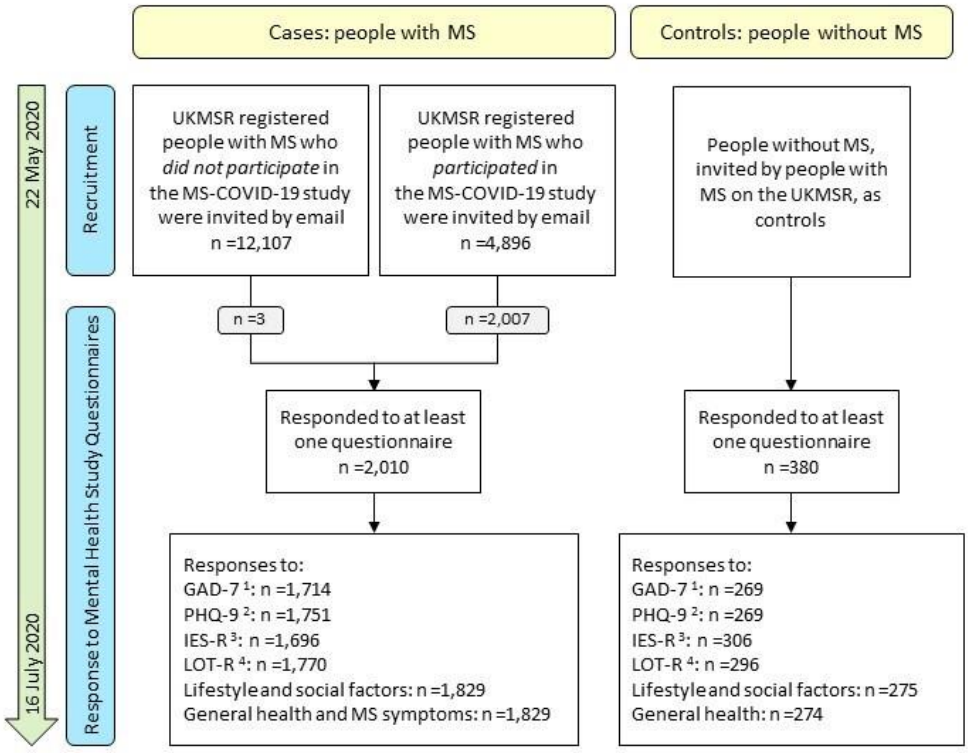
5.3. Patients and Methods

5.3.1. Study Design, Setting and Participants

The MS-COVID-19 study is an ongoing community-based, prospective and longitudinal cohort study conducted as part of the UKMSR (ClinicalTrials.gov: NCT04354519).[10] The UKMSR has been collecting patient-reported data from people with MS since 2011.[11] For the MS-COVID-19 study, we have been collecting COVID-19 related data from people with MS using online self-administered questionnaires since 17th March 2020—the beginning of the COVID-19 outbreak in the UK.

On 22nd May 2020, we invited people with MS registered with the UKMSR (including those who were taking part in the MS-COVID-19 study) by email to

complete questionnaires about their mental health, its social and lifestyle determinants, and their general health on a one-off basis (Appendix 5-B). In addition, we provided them with a link to invite people without MS (controls) to complete these same questionnaires, adding a case-control component to the study. People with MS and controls who responded to at least one of the questionnaires were included in the study (i.e., participants of the mental health study). The study flow diagram is depicted in Figure 5.1.



[1] General Anxiety Disorder 7-item for assessment of anxiety
[2] Patient Health Questionnaire 9-question for assessment of depression
[3] Impact of Events Scale-Revised for assessment of post-traumatic stress disorder
[4] Revised Life Orientation Test for assessment of optimism

Figure 5.1. Flow diagram of the MS-COVID-19 mental health study of the UKMSR.

In this paper, we report cross-sectional findings on the mental health of people with MS, its determinants, and their general health during the

outbreak (22nd May 2020 to 16th July 2020) and compare them to controls. We also report longitudinal findings on anxiety and depression levels of people with MS pre-COVID-19 (28th February to 1st April 2019 and 3rd September to 1st October 2019) and post-COVID-19 (7th February to 12th May 2020). We report the study according to the STROBE guidelines.[12]

5.3.2. Ethical Approval and Consent

Ethical approval for UKMSR studies was obtained from Southwest-Central Bristol Research Ethics Committee (16/SW/0194). The case-control study received separate ethical approval from the Departmental Ethics Committee (4913-4902). Participants provided informed consent online.

5.3.3. Data Collection

5.3.3.1. The UKMSR data

The UKMSR holds demographic data (age, gender, ethnicity), clinical data (type of MS, MS disease duration from diagnosis, DMTs), webEDSS scores[13] and HADS scores of registered people with MS.[14] We used the last webEDSS scores collected from 9th February 2017 to 3rd August 2020 to measure physical disability in people with MS. We used HADS scores for anxiety (HADS-A) and depression (HADS-D) among people with MS to compare their anxiety and depression levels during the outbreak to the year before. We considered a HADS score ≥11 as probable caseness of anxiety or depression (referred to as having HADS-anxiety or HADS-depression, here).[15] HADS scores for controls were not available.

5.3.3.2. The MS-COVID-19 study data

In the MS-COVID-19 study, we asked people with MS whether they were self-isolating and whether they had symptoms suggestive of a diagnosis of COVID-19.[10] These data were not available for controls.

5.3.3.3. Mental health questionnaires

We used the General Anxiety Disorder 7-item (GAD-7) and Patient Health Questionnaire 9-question (PHQ-9) scales to assess anxiety and depression, respectively, among people with MS and controls during the outbreak.[16 17] We used a cut-off of ≥10 for probable caseness of anxiety or depression (referred to as having anxiety or depression, here).[15]

We used the Impact of Event Scale—Revised (IES-R) to assess symptoms of post-traumatic stress disorder (PTSD) in people with MS and controls during the outbreak.[18] We considered scores ≥33 as probable caseness of PTSD (referred to as having PTSD, here).[18] We considered the IES-R subscales, including avoidance, hyperarousal, and intrusion in the analysis.[18]

To measure optimism during the outbreak, we used the Revised Life Orientation Test (LOT-R) scale with higher scores indicating more optimism.[19]

5.3.3.4. Social and lifestyle determinants of mental health questionnaires

We developed a questionnaire to assess whether participants had any changes (better/worse) in their lives related to social (relationships, social support, work, and feeling of loneliness) and lifestyle (exercise, diet, smoking,

and alcohol intake) factors during the outbreak compared to the year before. Participants used a visual analogue scale to indicate the change, with *no change* in the middle (45–55), *better* to the right (56–100), and *worse* to the left (0–44).

5.3.3.5. General health and MS symptoms questionnaires

We asked participants to report how their general health and (only for people with MS) MS symptoms had changed during the outbreak compared to the year before. We developed a similar questionnaire as described above.

5.3.4. Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA; 2017) and R (R Core Team, 2019).

5.3.4.1. Cross-sectional analysis

Continuous variables were assessed for normality of distribution by visual inspection of data. Data were analysed using the Mann-Whitney *U* test and presented as median (IQR) when not normally distributed and using the *t* test and presented as mean (SD) when normally distributed. The Mann-Whitney *U* test was also used for assessing ordinal variables. To assess the association between categorical variables, the $\chi 2$ (Chi-square) test was used (Fisher exact test when expected count ≤ 5).

For comparisons between people with MS and controls, multivariable logistic regression analysis was used—binomial or multinomial, based on the

dependent variable. To ascertain the association between mental health variables or having had COVID-19 and changes in general health or MS symptoms, multivariable multinomial logistic regression analysis was used. In each regression analysis, no change in the outcome was set as the reference value.

DAGs were built to determine potential confounding factors for individual regression analyses (Appendix 5-C).[20] A separate DAG was used for each exposure and outcome analysis model.[20] We chose this approach to avoid introducing bias by controlling for colliders and mediators in the regression analyses models which is a common issue in psychological research.[21] Confounding factors controlled for in each analysis have been stated in the results, and where not mentioned, adjustments for age, gender, and ethnicity were made. Listwise deletion was implemented for missing data. The number of cases included in each regression analysis has been indicated where there was missing data. The results of the regression analyses are presented as OR and 95% CIs.

5.3.4.2. Longitudinal analysis

The HADS scores of people with MS before and during the outbreak were compared using the Mann-Whitney *U* test (paired). The proportion of people with MS with HADS-anxiety or HADS-depression before and during the outbreak were compared using the McNemar test.

5.4. Results

5.4.1. Participants

A total of 2,010 people with MS and 380 controls were included in the study (Figure 5.1). Characteristics of people with MS (participants and nonparticipants from the total UKMSR population) and controls are presented in Table 5.1. A total of 2,226 people with MS on the UKMSR had provided a HADS score both during and before the outbreak (1,165 were participants of the mental health study).

Table 5.1. Demographic and clinical characteristics of participants and nonparticipants (from the total UKMSR population) of the MS and COVID-19 mental health study.

	Participants [a]		**Nonparticipants** [a]
	People with MS	**Controls**	**People with MS**
	n = 2,010	n = 380	n = 17,003
Age median (IQR), years	56 (48–63) n = 2,006	49 (37–61) [d] n = 340	53 (44–62) [d] n = 14,993
Women n (%)	1,488 (74.3)	248 (73.6)	11,089 (74.0)
White ethnicity n (%)	1,942 (81.8)	329 (97.1)	13,240 (96)
Smoker [b] n (%)	160 (8.7)	20 (7.2)	409 (23.8) [d]
Alcohol intake [b] n (%)	1,141 (62.4)	216 (77.7) [d]	NA
MS-related factors			
RRMS: PMS n	1,114: 781	NA	7,031: 4,475
MS disease duration median (IQR), years	12 (6–20) n = 1,975	NA	12 (7–20) n = 13,094

	Participants [a]		Nonparticipants [a]
	People with MS	**Controls**	**People with MS**
	n = 2,010	n = 380	n = 17,003
Taking DMTs n (%)	862 (42.9)	NA	2,034 (51.1) [d]
WebEDSS median (IQR)	5.5 (3–6.5) n = 1,679	NA	5.5 (3–6.5) n = 5,628
HADS-A score [b] median (IQR)	6 (3–9) n = 1,350	NA	7 (3–10) [d] n = 1,553
with anxiety [b, c] n (%)	251 (18.6)	NA	369 (23.8) [e]
HADS-D score [b] median (IQR)	6 (3–10) n = 1,350	NA	6 (3–10) n = 1,553
with depression [b, c] n (%)	282 (20.9)	NA	328 (21.1)
With anxiety and/or depression [b, c] n (%)	385 (28.5)	NA	496 (31.9)

HADS = Hospital Anxiety and Depression Scale (HADS-A for anxiety and HADS-D for depression); RRMS = Relapsing-Remitting MS; PMS = Progressive MS (includes primary and secondary progressive types of MS); DMTs = Disease-Modifying Therapies; NA = Not Applicable or Not Available; UKMSR = United Kingdom MS Register; WebEDSS = Web-based Expanded Disability Status Scale

[a] Participants with missing data have been excluded from the analysis for each variable separately.

[b] Before the COVID-19 outbreak.

[c] HADS score ≥11 was considered as probable caseness of anxiety or depression

[d] *p* value compared to people with MS (participants) <0.001

[e] *p* value compared to people with MS (participants) =0.001

5.4.2. Anxiety, Depression and PTSD

Mental health characteristics of people with MS and controls are presented in Table 5.2.

Table 5.2. Mental health characteristics of participants of the MS-COVID-19 mental health study during the COVID-19 outbreak.

	People with MS	**Controls**	***p* value**
GAD-7 median (IQR)	4 (1–8) n = 1,714	4 (1–7) n = 269	0.81
With anxiety [a] n (%)	334 (19.5)	45 (16.7)	0.29
PHQ-9 median (IQR)	6 (3–12) n = 1,751	5 (2–9) n = 269	0.002
With depression [a] n (%)	573 (32.7)	64 (23.8)	0.003
With anxiety and/or depression [a] n (%)	632 (36.8) n = 1,781	73 (27.1) n = 269	0.002
IES-R median (IQR)	16 (6–32) n = 1,696	20 (10–33) n = 306	0.01
With symptoms of PTSD [a] n (%)	398 (23.5)	77 (25.2)	0.52
IES-R subscales median (IQR)			
Avoidance (Scored 0–32)	7 (2–13) n = 1,790	8 (4–13) n = 307	0.06
Hyperarousal (Scored 0–24)	4 (1–8) n = 1,797	4.5 (1–9) n = 306	0.06
Intrusion (Scored 0–32)	5 (1–11) n = 1,797	7 (3–12) n = 307	0.001
LOT-R (Scored 0–24) median (IQR)	12 (10–13) n = 1,770	14 (10–18) n = 296	<0.001

GAD-7 = General Anxiety Disorder 7-item; PHQ-9 = Patient Health Questionnaire 9-questions; IES-R = Impact of Event Scale-Revised; PTSD = Post-Traumatic Stress Disorder; LOT-R = Revised Life Orientation Test

[a] GAD-7 ≥10 (scored 0-21), PHQ-9 ≥10 (scored 0-27), and IES-R ≥33 (scored 0-88) are regarded as experiencing symptoms indicative of probable cases of anxiety, depression, and PTSD, respectively.

People with MS were more likely to have anxiety and/or depression during the outbreak than controls (n = 1,982; OR: 2.14, 95% CI: 1.57–2.91). The likelihood of having PTSD in people with MS during the outbreak was not different from controls (n = 1,996; OR: 1.13, 95% CI: 0.84–1.52).

The HADS scores of people with MS during the outbreak had not significantly changed from their last score the year before (Table 5.3).

Table 5.3. HADS-A and HADS-D scores (scored 0-21) of people with MS during the COVID-19 outbreak and the year before the outbreak.

	During the outbreak vs anytime the year before			**During the outbreak vs same period the year before**		
	Before [a]	**During** [b]	***p***	**Before** [c]	**During** [b]	***p***
Registered with the UKMSR	n = 2,226			n = 336		
HADS-A median (IQR)	6 (3–10)	6 (3–10)	0.87	7 (3–10)	7 (3–10)	0.91
with anxiety [d] n (%)	463 (20.8)	470 (21.1)	0.72	77 (22.9)	81 (24.1)	0.69
HADS-D median (IQR)	6 (3–10)	7 (3–10)	0.23	7 (4–10)	7 (4–10)	0.68
with depression [d] n (%)	470 (21.1)	475 (21.3)	0.81	79 (23.5)	69 (20.5)	0.20
With anxiety and/or depression [d] n (%)	660 (29.6)	658 (29.6)	0.96	110 (32.7)	106 (31.5)	0.72

	During the outbreak vs anytime the year before			During the outbreak vs same period the year before		
	Before [a]	**During** [b]	***p***	**Before** [c]	**During** [b]	***p***
Participants of the mental health study	n = 1,165			n = 114		
HADS-A median (IQR)	6 (3–9)	6 (3–9)	0.49	6 (2–9)	6 (3–9)	0.63
with anxiety [d] n (%)	207 (17.8)	214 (18.4)	0.61	17 (14.9)	23 (20.2)	0.24
HADS-D median (IQR)	6 (3–10)	6 (3–10)	0.63	7 (3.75–10)	7 (4–10)	0.89
with depression [d] n (%)	235 (20.2)	246 (21.1)	0.39	23 (20.2)	22 (19.3)	1
With anxiety and/or depression [d] n (%)	317 (27.2)	324 (27.8)	0.65	30 (26.3)	31 (27.2)	1

HADS = Hospital Anxiety and Depression Scale; HADS-A = HADS for anxiety; HADS-D = HADS for depression; UKMSR = United Kingdom MS Register

[a] Most recent response from 28 February to 1 April 2019 or 3 September to 1 October 2019

[b] Most recent response from 7 February to 12 May 2020

[c] Most recent response from 28 February to 1 April 2019

[d] HADS score ≥11 was considered as probable casesness of anxiety or depression.

Having had COVID-19 was not associated with having anxiety and/or depression during the outbreak (after the infection, if present) (OR: 1.43, 95% CI: 0.75–2.74) (n = 1,128; adjusted for age, gender, ethnicity, webEDSS, self-isolation, taking DMTs, and HADS-anxiety and/or HADS-depression before the

outbreak). HADS-anxiety and/or HADS-depression before the outbreak did not predict self-reporting COVID-19 among people with MS (OR: 1.04, 95% CI: 0.73–1.48) (n = 2,655; adjusted for age, gender, webEDSS and taking DMTs).

5.4.3. General Health and MS Symptoms

A total of 1,829 people with MS and 274 controls responded to the change in general health question, and 1,829 people with MS responded to the change in MS symptoms question (Table 5.4).

Table 5.4. Changes in general health and MS symptoms during the COVID-19 outbreak compared to before the outbreak.

	People with MS n (%)	**Controls** n (%)	***p* value** [a]
Changes in General Health			
No change	863 (47.2)	142 (51.8)	<0.001
Worse	754 (40.7)	74 (27)	
Better	221 (12.1)	58 (21.2)	
Changes in MS Symptoms			
No change	979 (53.5)	NA	NA
Worse	758 (41.4)	NA	
Better	92 (5)	NA	

NA = Not Applicable or Not Available
[a] $\chi 2$ (Chi-square) test

People with MS were more likely than controls to report a decline in their general health during the outbreak compared to before (OR: 1.95, 95% CI: 1.43–2.65). In a post hoc analysis, we compared this outcome (decline in general health) between people with MS and controls separately within two groups: (1) participants with anxiety and/or depression and (2) participants

without anxiety or depression. Among participants without anxiety or depression (n = 1,263), the findings were similar: people with MS had a higher likelihood of a decline in general health than controls (OR: 1.79, 95% CI: 1.16–2.76). However, among participants with anxiety and/or depression (n = 673), there was no difference between people with MS and controls in reporting a decline in general health (OR: 1.51, 95% CI: 0.86–2.65).

Among only people with MS, the general health of participants with anxiety and/or depression during the outbreak was more likely to deteriorate than those without anxiety or depression (OR: 3.59, 95% CI: 2.71–4.76) (n = 1,398; adjusted for age, webEDSS, self-reported COVID-19, LOT-R and changes in loneliness).

People with MS with COVID-19 were more likely to report deterioration in their general health than those without COVID-19 (OR: 1.99, 95% CI: 1.07–3.69) (n = 1,055; adjusted for age, gender, ethnicity, webEDSS, taking DMTs, self-isolation, and changes in HADS-A and HADS-D from before the outbreak).

People with MS with anxiety and/or depression during the outbreak were more likely to report worsening of their MS symptoms compared to those without anxiety or depression (OR: 5.23, 95% CI: 4.16–6.57) (n = 1,611; adjusted for taking DMTs, MS type, COVID-19 and LOT-R).

Having had COVID-19 predicted a higher likelihood of MS symptoms worsening (OR: 1.97, 95% CI: 1.06–3.67) (n = 1,052; adjusted for age, gender,

ethnicity, webEDSS, taking DMTs, self-isolation, and changes in HADS-A and HADS-D from before the outbreak).

5.4.4. Social and Lifestyle Determinants of Mental Health During the Outbreak

Changes in social and lifestyle factors of people with MS and controls during the outbreak are presented in Table 5.5.

Table 5.5. Changes in social and lifestyle determinants of mental health during the COVID-19 outbreak compared to before the outbreak.

	People with MS n (%)	**Controls** n (%)	***p* value** [a]
Change in Relationships			
The same	1,042 (57)	133 (48.7)	<0.001
Worse	393 (21.5)	45 (16.5)	
Better	394 (21.5)	95 (34.8)	
Change in Social Support			
The same	821 (44.9)	122 (44.5)	0.01
Worse	265 (14.5)	23 (8.4)	
Better	743 (40.6)	129 (47.1)	
Change in Loneliness			
The same	857 (46.9)	138 (50.5)	0.51
Feeling lonelier	843 (46.1)	118 (43.2)	
Feeling less Lonely	129 (7.1)	17 (6.2)	
Change in Work			
Yes	372 (20.3)	81 (29.5)	0.001
No	1,457 (79.7)	194 (70.5)	
Change in Income			
The same	1,087 (59.4)	164 (59.9)	0.88
Less	582 (31.8)	84 (30.7)	
More	160 (8.7)	26 (9.5)	

	People with MS n (%)	Controls n (%)	*p* value [a]
Change in Exercise			
The same	538 (29.4)	81 (29.6)	<0.001
Worse	766 (41.9)	80 (29.2)	
Better	525 (28.7)	113 (41.2)	
Change in Diet			
The same	750 (41)	82 (30)	<0.001
Worse	704 (38.5)	108 (39.6)	
Better	375 (20.5)	80 (30.4)	
Change in Smoking			
The same	55 (34.4)	9 (45)	0.54 [b]
More	30 (18.8)	2 (10)	
Less	75 (46.9)	9 (45)	
Change in Alcohol Intake			
The same	550 (48.2)	78 (36.4)	<0.001
More	244 (21.4)	29 (13.6)	
Less	347 (30.4)	107 (50)	

[a] χ2 (Chi-square) test
[b] Fisher exact test

People with MS were more likely to feel lonelier than controls (OR: 1.36, 95% CI: 1.04–1.80). Among people with MS with anxiety and/or depression during the outbreak, 73.3% (n = 442) reported feeling lonelier as opposed to 31.5% (n = 340) of those without anxiety or depression ($p < 0.001$). The findings were similar among people with MS with and without HADS-anxiety and/or HADS-depression before the outbreak (60.5% (n = 214) vs 37.2% (n = 336) felt lonelier, $p < 0.001$).

People with MS were more likely to experience worsening of their social support than controls (OR: 1.90, 95% CI: 1.18–3.07). A larger proportion of people with MS with anxiety and/or depression during the outbreak reported worsening of their social support than those without anxiety or depression (23.9% (n = 144) vs 9.5% (n = 103), $p < 0.001$)—similar to those with and without HADS-anxiety and/or HADS-depression before the outbreak (24% (n = 85) vs 11% (n = 99), $p < 0.001$). The likelihood of experiencing worse relationships during the outbreak among people with MS was not significantly different from controls (OR: 1.35, 95% CI: 0.93–1.96), but people with MS were less likely to report having better relationships compared to before the outbreak (OR: 0.65, 95% CI: 0.48–0.88).

The exercise habits of people with MS were more likely to become worse than controls (OR: 1.65, 95% CI: 1.18–2.32). Among people with MS, HADS-anxiety and/or HADS-depression before the outbreak was associated with worsening of exercise during the outbreak (OR: 1.38, 95% CI: 1.03–1.86). A higher webEDSS score among people with MS was not significantly associated with worsening of exercise (OR: 1.03, 95% CI: 0.96–1.11), but predicted a lower likelihood of having better exercise during the outbreak than before (OR: 0.77, 95% CI: 0.71–0.84) (n = 1,541; adjusted for age, gender, taking DMTs, and MS type). Controls were more likely to have improved their diet than people with MS during the outbreak (OR: 1.64, 95% CI: 1.16–2.32).

People with MS were not significantly different from controls in terms of having undergone a change in their work (OR: 0.80, 95% CI: 0.59–1.08). A

higher webEDSS score predicted a lower likelihood of undergoing a change in work among people with MS (OR: 0.86, 95% CI: 0.80–0.92) (n = 1,541; adjusted for age, gender, MS type and taking DMTs). Among participants whose work had changed, people with MS were more likely to report being more stressed by this change than controls (OR: 2.40, 95% CI: 1.12–5.18). People with MS with and without anxiety and/or depression during the outbreak were not significantly different in feeling more stressed due to a change in work (OR: 1.29, 95% CI: 0.64–2.60). The absence of anxiety and depression among people with MS, however, was associated with a higher likelihood of feeling less stressed due to a change in work (OR: 3.64, 95% CI: 1.95–6.80) (n = 347; adjusted for changes in support, relationships and income).

Compared to controls, people with MS were more likely to experience a reduction in their income during the outbreak (OR: 1.41, 95% CI: 1.04–1.90). Among participants who underwent a change in work, there was no significant difference between people with MS and controls in having a reduction (OR: 1.09, 95% CI: 0.63–1.88) or increase in income (OR: 0.89, 95% CI: 0.39–2.06).

5.5. Discussion

Our findings add to the evidence that people with MS are more likely to experience anxiety and depression than the general population.[5 6] This study on a large national population of people with MS covers the first lockdown in

the UK, which started on 23rd March 2020 and was eased on 4th July 2020. We did not find a significant change in the levels of anxiety and depression among people with MS during this period compared to the year before, which is consistent with the results of other studies.[22-24] Taken together, these findings suggest that the differences we, and others,[24 25] have found in anxiety and depression between people with MS and those without MS during the outbreak were most likely due to MS-related factors rather than the outbreak at the early phases of the pandemic. Studies of the general population have shown that levels of psychological distress have increased during the pandemic and people with higher risk of COVID-19, young adults, women and populations with pre-existing mental or physical health conditions have fared even worse.[3 26] Given that people with MS meet one or more of these conditions, we have considered why their anxiety and depression levels have not changed in line with general population surveys. One reason could be because people with MS are resilient,[22] or because support systems were already in place for people with MS and these were agilely mobilised to address the concerns of this population quickly when the pandemic started (e.g. the local branches of the UK MS Society, which has peer-support groups and had a helpline that was available for people with MS).[27] More than 85% of people with MS in our study reported that the social support they received before the outbreak had improved or had not changed during the outbreak. We do not know whether the pandemic will have a more profound effect on people with MS in the future. Studies should

continue to monitor the mental wellbeing of people with MS throughout the pandemic and thereafter.

Poor mental health has a negative impact on the quality of life, and physical and cognitive function of people with MS.[28] The study found that anxiety and depression have a substantial negative effect on the general health of people with MS and their MS symptoms, which can be greater than the impact of COVID-19. This points to a need for MS services to provide continued targeted multidisciplinary psychological support for this population.

We found that many people with MS were feeling lonelier during the outbreak than before, and they were more likely to feel this way if they had anxiety or depression. People with MS were slightly more likely than people without MS to feel lonelier during the outbreak. The observations that loneliness is linked with poor health-related outcomes and depression,[29-31] along with our findings, point to a need to address loneliness among people with MS during periods of lockdown. Interventions for homebound older adults, that improve social connectedness and reduce depressive symptoms and disability,[32] could be adapted for people with MS.

Many people with MS did not experience any changes in their social support, relationships, work or income after the outbreak, suggesting that the response of the MS community to the unforeseen transformations at the early stages of the pandemic was effective. The lockdown also had potential benefits to people with MS which have been pointed out by other authors.[22]

However, when there was a change in these social factors, people with MS were affected more adversely than those without MS.

The restrictions imposed by the pandemic limited the physical activity of people with MS and did not provide them the opportunity to develop better diets compared to people without MS. Therefore, people with MS appear to be more susceptible to the adverse effects of the outbreak on lifestyle. These are important aspects for clinicians to assess and address in routine encounters because improving lifestyle factors (such as exercise) can improve the mental and physical health of people with MS.[33 34]

Our results confirm that anxiety and depression in people with MS are not specific to the COVID-19 era: they have remained high before and during the pandemic. Social and lifestyle factors have an undeniable role in mental health,[6-9] but these factors changed in different directions among our study population of people with MS (e.g. some felt lonelier while others received better social support during the outbreak) which could have resulted in the stable anxiety and depression levels observed among people with MS.

It is not uncommon for mental health conditions to go undetected.[35] There is scope for effective management of anxiety and depression in people with MS, and modifications in lifestyle and social factors may provide additional benefits to their health-related quality of life.[36 37] Therefore, it is vital that clinicians routinely screen for mental health problems, particularly in this COVID-19 era, and refer people with MS to appropriate wellbeing or mental

health services for further assessment and support. It is also important that the MS community is aware of their specific vulnerabilities, so that they can take steps to proactively seek support.

5.5.1. Limitations of the Study

We cannot precisely calculate our response rate (in people with MS and controls) as we do not know how many people received the study emails. This is a common limitation in studies that recruit participants through registries or social media.[26] We tried to increase our recruitment by advertising the study and sending reminder emails.[38] Nevertheless, we have studied a large national population of people with MS—the largest among current (i.e., at the time of manuscript submission) COVID-19 and mental health studies among people with MS.

The mental health study MS sample had slightly lower levels of anxiety than nonparticipants from the UKMSR and, therefore, their response to the pandemic could have been different. Nevertheless, our findings are in keeping with the results of similar studies.[22-24]

Different cut-offs have been recommended to identify caseness of anxiety and depression using HADS.[39] Here, we used a priori cut-offs based on a validation study in MS.[15]

Failure to find a difference between HADS scores before and during the outbreak might be influenced by seasonal effects on experiencing anxiety and

depression symptoms. Changes in HADS score could not be tested for each season in 2019 and 2020 separately because of small sample sizes.

The UKMSR was not collecting data on social and lifestyle determinants of mental health (as assessed in this study) before the COVID-19 outbreak. Therefore, we were unable to directly compare these factors during and before the outbreak. We tried to overcome this problem by asking participants about changes in these factors during the COVID-19 outbreak compared to before.

We asked people with MS to invite people without MS (controls) to the study who could be their friends and relatives, sharing similar social networks or living in similar neighbourhoods with similar socioeconomic status. This can be a strength in that the controls and people with MS are similar but could also lessen the actual difference between their mental health status. However, the proportion of controls who had anxiety and/or depression in our study (27.1%) is comparable to findings among the UK general population during the same period (27.3%).[3]

We included self-reported COVID-19 instead of confirmed cases since the sample size for the latter was small. However, people with MS with anxiety and/or depression did not tend to report having had COVID-19 any more than people with MS without anxiety or depression.

We could not study the association between ethnicity and mental health because the number of people from ethnic backgrounds other than White ethnicity in the UKMSR was small.

5.5.2. Up-to-date Literature Review

Following the publication of this article, a meta-analysis of 113 studies was performed, which corroborated the results of the above UKMSR study: Although people with MS had higher levels of anxiety and depression compared to the general population, their levels of anxiety and depression had remained the same before and during the COVID-19 pandemic.[40] In addition, studies had not found a change in the mental and physical quality of life of people with MS before and during the pandemic.[40] As discussed above, these findings could be because people with MS are resilient,[22] or because they had reached a *ceiling effect*—i.e., they were already experiencing high levels of anxiety and depression before the COVID-19 pandemic that could not significantly deteriorate any further.[40]

5.6. References

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Chapter 6

The Application of Directed Acyclic Graphs in Regression Analysis

6. The Application of Directed Acyclic Graphs in Regression Analysis

6.1. The Rationale

Regression analysis is used to show the relationship between one dependent variable and at least one independent variable.[1] In this text, the dependent and independent variables are referred to as the *outcome* and the *exposure*, respectively.[2] The relationship between two variables is often more complex than a unidirectional path from an exposure to an outcome, with one or more confounders (Figure 6.1) that need to be adjusted for in the regression analysis.[2 3] There are also colliders and mediators (Figure 6.1) that should not be included in the regression analysis.[2 3]

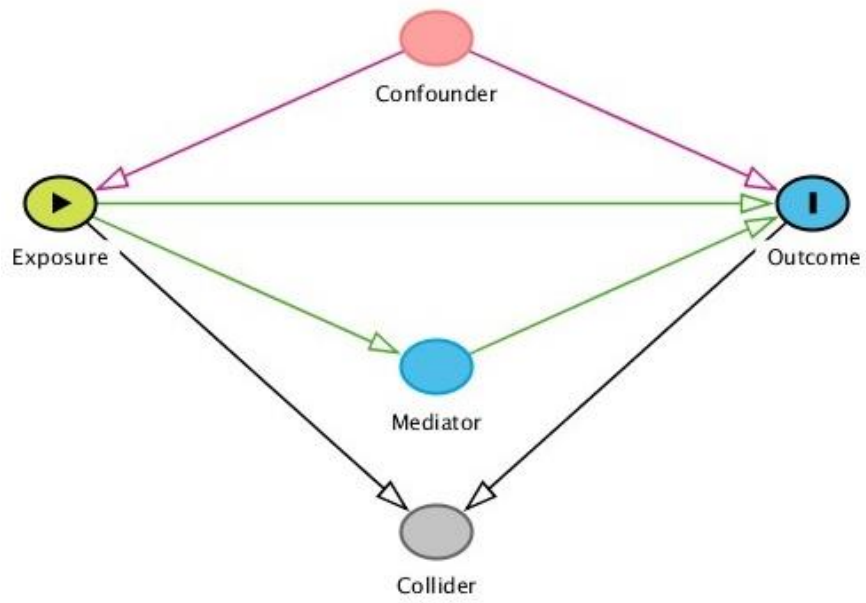

Figure 6.1. A directed acyclic graph (DAG) depicting the relationships between different variables. The DAG was constructed using DAGitty (https://www.dagitty.net/).

It is evident that deciding the nature of the outcome and exposure variables is at the discretion of the investigator; selecting confounders, colliders, and

mediators should be no exception.[2] The following elaboration on confounders, colliders, mediators, and their corresponding biases highlights the importance of considering the causal structure of an observational study before performing a regression analysis.[4] An overly simplified schematic diagram of these biases, as detailed below, is presented in Figure 6.2.

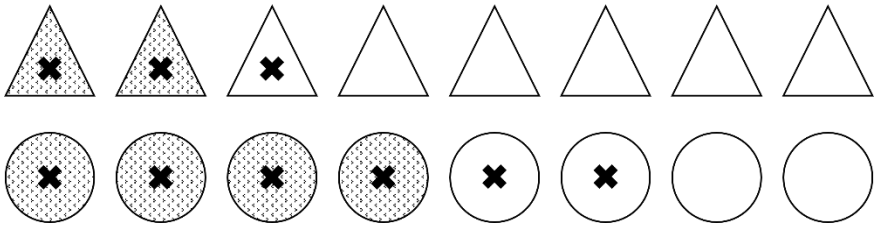

Figure 6.2. Schematic diagram depicting confounding and collider biases. The examples are oversimplified and do not necessarily reflect the findings of this thesis.
Confounding bias: Triangles (Δ) = people with MS *without* anxiety and/or depression. Circles (O) = people with MS *with* anxiety and/or depression. Patterned shapes = people with delayed recovery from COVID-19 in both groups. Cross marks = people with high webEDSS scores in both groups. 25% of Δ have delayed recovery from COVID-19 vs 50% of O. Adjusting for webEDSS scores will show that among people with high webEDSS scores the rate of delayed recovery from COVID-19 is 66.7% in both Δ and O. In this case, adjustment for webEDSS scores is necessary as it affects the chances of having both anxiety and/or depression and delayed recovery from COVID-19.
Collider bias: Δ = people *without* MS. O = people with MS. Patterned shapes = people with a decline in their general health during the COVID-19 outbreak in both groups. Cross marks = people with worse exercise habits during the outbreak in both groups. 25% of Δ have a decline in their general health vs 50% of O. In this case, adjusting for worse exercise habits will show that among people with worse exercise habits the rate of experiencing a decline in general health is 66.7% in both Δ and O, making the wrong impression that worse exercise habits have caused the decline in general health in a very short period.
WebEDSS = Web-based Expanded Disability Status Scale

In a causal model, a confounder is a variable that (1) causes the outcome, (2) causes or is associated with the exposure, and (3) is not caused by the exposure (Figure 6.1).[2 3 5] Failure to adjust for a confounder in a regression

analysis will bias the results, by mixing the relationship between the exposure and the outcome with the effect of the confounder on the outcome (Figure 6.2).[5]

The following example is from Chapter 4, 'Recovery from COVID-19 in Multiple Sclerosis'.[6] One of the objectives of this study was to estimate the effect of having anxiety and/or depression among people with MS on the time they needed to recover from COVID-19. The multivariable Cox regression analysis showed that having anxiety and/or depression delays recovery from COVID-19 (Table 4.3). A causal model was elicited before carrying out any analysis (Appendix 4-C). As depicted in the model (Appendix 4-C), a person's level of physical disability (measured using the webEDSS) may affect their mental health status as well as their capacity to recover from COVID-19; hence, acting as a confounder in the above relationship. People with high webEDSS scores may be more likely to have anxiety and/or depression. Moreover, people with high webEDSS scores may be more likely to experience a slower recovery from COVID-19, regardless of their mental health status. Failure to adjust for the level of physical disability in the analysis would have created a study population consisting of people with different webEDSS scores in which more people with high webEDSS scores have anxiety and/or depression than those with low webEDSS scores. In this situation, it would have been impossible to decide whether a high webEDSS score, having anxiety and/or depression, or both have delayed the recovery from COVID-19. In other words, the negative effect of having anxiety and/or

depression on recovery from COVID-19 would have been overestimated (Figure 6.2).

A collider is a variable that is affected by both the exposure and the outcome (Figure 6.1).[7-9] Adjusting for a collider in a regression analysis will introduce bias into the results by restricting the study population to this variable (Figure 6.2).[7-9]

In Chapter 5, 'Mental Health of People with Multiple Sclerosis During the COVID-19 Outbreak', multivariable regression analysis was used to estimate the likelihood of experiencing a decline in general health during the COVID-19 outbreak in people with MS compared to those without MS; people with MS were more likely to report a decline in their general health.[10] The causal model (Appendix 5-C) revealed a change in exercise habits to be a collider in the above relationship, as both having MS and a decline in general health, presumably, can have an adverse effect on this variable. Adjusting for a change in exercise habits in the regression analysis would have restricted the study population to those with a certain change in this variable. For example, if the analysis was restricted to people with worse exercise habits during the COVID-19 outbreak, a large proportion of people without MS included in the analysis would have had a decline in their general health. As a result, the difference between people with and without MS in reporting a decline in their general health would have been minimised (Figure 6.2). The relationship could have even been reversed if the decline in general health had affected the exercise habits of people without MS more so than people with MS, for

instance: people with MS who were likely to experience a decline in their general health did not exercise before and continued not to do so during the outbreak (so, reported no change in their exercise habits), but people without MS had been physically active before but did not exercise during the outbreak as a result of a decline in their general health. In this scenario, a larger proportion of the population of people with worsening of their exercise habits would have consisted of people without MS with a decline in their general health than people with MS and a decline in their general health.

As the name indicates, a mediator is a variable that mediates the causal relationship between an exposure and an outcome (Figure 6.1).[3] The mediator explains the *indirect effect* of the exposure on the outcome (Figure 6.1).[11 12] Adjusting for the mediator in a regression analysis would remove this indirect effect, and, consequently, the analysis will measure the *direct effect* of the exposure on the outcome, unexplained by the mediator.[11 12] This is the basis for mediation analysis,[11 12] which is beyond the scope of this thesis. The regression analyses in this thesis were devised to estimate the *total effect* (i.e., the direct and indirect effects) of an exposure on an outcome.

The following is another example from Chapter 4, 'Recovery from COVID-19 in Multiple Sclerosis'.[6] The study found that people with MS with webEDSS scores of 7 or higher required more time to recover from COVID-19. As presented in the causal model (Appendix 4-C), hospitalisation due to COVID-19 was identified as a mediator in the relationship between the level of physical disability and recovery from COVID-19. Adjusting for hospitalisation

in the multivariable Cox regression analysis would have removed its mediating effect from the result, by eliminating people with MS who both had a high webEDSS score and had been hospitalised due to COVID-19 from the analysis. As a result, the adverse effect of physical disability on recovery from COVID-19 would have been biased.

At this stage, it can be appreciated that adjusting for any of the above variables (i.e., a confounder, collider, or mediator) in a regression analysis will generate the same effect from a mathematical perspective (Figure 6.2).[11] It is the conceptual understanding of how the adjustments will impact the interpretation of the results that determines whether a given adjustment is necessary or harmful (Figure 6.2).[2 11] It is, therefore, crucial that the causal relationships between variables of an observational study are established before any statistical analysis.

6.2. Eliciting a Directed Acyclic Graph

Directed acyclic graphs (DAGs) are increasingly being used to portray the causal relationships between a set of variables and inform study design and statistical analysis for developing prediction models.[13-15] Within the scope of this thesis, the following will discuss the application of DAGs in observational studies to select variables that should be included in a regression analysis to predict, as accurately as possible, the odds of the occurrence of an outcome based on a given exposure.

A DAG represents the causal inferences between measured and, in some cases, unmeasured variables of an observational study, and is constructed based on a priori knowledge and assumptions about these causal associations.[13 14] A DAG enables the identification of potential sources of bias (i.e., confounders, colliders, and mediators, as discussed above in section 6.1. The Rationale) and provides a *minimal sufficient adjustment set* of confounding variables to include in the regression analysis for estimation of the total effect of an exposure on an outcome.[2 14]

A causal diagram is composed of *nodes*, which represent the variables, and *arrows* that directly connect two nodes and depict the causal relationship between the variables (Figure 6.1).[2] Variables can, therefore, be connected through *paths* of single (e.g., Exposure → Outcome in Figure 6.1) or multiple (e.g., Exposure → Mediator → Outcome in Figure 6.1) arrows.[2] A causal diagram becomes a DAG if it is (1) directed: all nodes are connected by arrows and not by nondirectional lines (without arrowheads), which indicate an association between two variables without any cause-and-effect relationship, and (2) acyclic: there is no path that forms a closed loop, starting from and ending on the same variable—a variable cannot cause itself.[2 16]

DAGs are most conveniently created using computer programmes.[17] DAGitty is one of the most widely used programme, which was also used in this thesis; it is an open-source web-based application that is accessible at *www.dagitty.net*. This software will automatically apply all the criteria for identifying confounders in a DAG. The website includes a detailed tutorial

about building DAGs in the DAGitty environment and using them to determine the minimal sufficient adjustment set for estimating any given exposure-outcome relationship in a multivariable regression analysis.

6.3. Strengths and Limitations of Directed Acyclic Graphs

The following is a brief discussion of some of the strengths and limitations of DAGs, a useful and promising tool for avoiding bias in clinical research that needs to be further developed.

The causal relationships depicted in a DAG are qualitative—they do not require quantitative analysis as structural equation models do,[16 18] and do not reflect the strength or the direction of the relationship (i.e., positive, or negative).[3] As previously indicated, DAGs are formed based on a priori knowledge and assumptions about the causal relationships between variables.[13 14] They are constructed as part of the statistical analysis plan before any knowledge of the collected data. This approach is contrary to the conventional stepwise multivariable regression analysis in which the variables included in/excluded from a model are selected based on the statistical significance of their effect on the outcome.[19] The results of the latter, thereby, may not be generalisable to a population out of the sample data and will potentially be biased because of the inclusion of colliders and mediators (that showed a statistically significant correlation with the outcome within the sample data) or the exclusion of confounders (that did not have a statistically significant correlation with the outcome within the sample data).[19]

Most often, what is deemed as 'high-quality evidence' derived from randomised clinical trials does not exist to support causation and observational data is all one has to draw causal inferences[14 16 20 21]—the connections between variables in a DAG are often correlation rather than causation.[16] In the absence of robust evidence from the literature, the causal relationships of a DAG may be based on 'inference to the best explanation' or expert opinion.[22 23] Various techniques have been proposed to mitigate these problems, and they merit a separate review.[17 21-23]

The application of DAGs in studies and their presentation in published articles promote transparency.[13 16] Eliciting a DAG requires in-depth thinking about the causal structure of a study and the relationships between measured and, equally important, unmeasured variables.[16 24] As a rule, the construction of a DAG starts with assuming bidirectional connections between all variables of a study, and then, individual connections are removed based on causal assumptions—it is often more challenging to conclude that two variables are not related.[13 21] This process (of deciding the variables and connections included in a DAG) necessitates engagement with other researchers, especially experts in each domain, and other stakeholders such as patients.[22] In this thesis, academic people with MS contributed to the design of the DAGs.[25] In addition to prompting researchers to critically reflect on their research,[14] the transparent presentation of DAGs and the adjustment sets they have yielded in published articles will enhance external scrutiny of the study,[13] which is the essence of scientific research. This approach opens a

dialogue about the causal assumptions of the researchers and allows a more accurate interpretation of the results.[13] Currently, the presentation of DAGs in published articles is not uniform and Tennant et al have proposed some recommendations to improve it.[13]

In some cases, a causal diagram will include several variables that are related via many different paths.[23] As a result, the causal diagram may form closed-loop paths that will impede its function to yield an adjustment set. This situation was encountered in the study, 'Mental Health of People with Multiple Sclerosis During the COVID-19 Outbreak', in Chapter 5 (Appendix 5-C). There are no clear guidelines for solving the issues related to a *saturated* DAG,[13] but in these instances, the researchers may have to compromise by deciding to keep the most relevant variables and the strongest associations for each exposure-outcome relationship and clearly reporting it.

6.4. Conclusion

The application of DAGs in study designs and statistical analyses has expanded—from observational studies to randomised clinical trials and from causation to diagnostic and prognostic models.[13 14] From computer sciences, DAGs have found their way into epidemiological, sociological, and psychological studies.[16 26] It will not be long before DAGs become a cornerstone of all clinical research. There is great variability in the current techniques used for constructing and presenting DAGs and they seem to be far from perfect.[13 21 23] This introduction to DAGs intended to highlight the

importance of using this tool in clinical research and improving it through the process. So far, the use of DAGs has been refined by researchers, mostly epidemiologists, who have implemented it. Tennant et al., in their review of the use of DAGs in applied health research, conclude that "[...] we welcome the large and growing number of applied health researchers who have used DAGs [...]. These 'early adopters' have not only helped to reveal some potential pitfalls in the use of DAGs but have provided a growing wealth of innovative exemplars that will inspire future developments in this evolving field".[13]

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Chapter 7

Impact of Mass Vaccination on SARS-CoV-2 Infections Among People with MS on Immunomodulatory Disease-Modifying Therapies in England

7. Impact of Mass Vaccination on SARS-CoV-2 Infections Among People with MS on Immunomodulatory Disease-Modifying Therapies in England

The published article[1] in included in Appendix 7-A.

7.1. Abstract

7.1.1. Background

Contradicting assumptions were made about the effectiveness of COVID-19 vaccines in people with MS receiving immunomodulatory DMTs based on the quantification of humoral and cellular immune responses. This study aimed to understand changes in the risk of the severe acute respiratory distress syndrome-coronavirus-2 (SARS-CoV-2) infection among the total population of people receiving MS DMTs in England following mass vaccination.

7.1.2. Methods

This is a retrospective analysis of national data collected prospectively and longitudinally. NHS England and NHS Improvement (NHSE/I) hold prescribing data on all commissioned MS DMTs in England. The UK Health Security Agency (UKHSA) has been collecting data on all registered SARS-CoV-2 test results, including RT-PCR and rapid antigen tests. All people receiving MS DMTs were identified using NHSE/I datasets. All people receiving MS DMTs with SARS-CoV-2 infection (i.e., positive test) from March 2020 to August 2021 were identified by merging NHSE/I and UKHSA datasets. Similar data for the general population were captured using publicly available datasets of the

UK government. The incidence rate ratios (IRR) of SARS-CoV-2 infection among people receiving MS DMTs compared to the general population during the pre-vaccination (November 2020 to January 2021) and post-vaccination (June to August 2021) periods were calculated.

7.1.3. Results

A mean (SD) of 41,208 (4,301) people received an MS DMT in England during each month from March 2020 to August 2021. The IRR (95% CI) of infection in people taking ocrelizumab versus the general population increased from 1.13 (0.97–1.31) during the pre-vaccination period to 1.79 (1.57–2.03) during the post-vaccination period. For people on fingolimod, it increased from 0.87 (0.73–1.02) to 1.40 (1.20–1.63) during the same periods. There were no significant changes for people on other MS DMTs.

7.1.4. Conclusion

COVID-19 vaccines offer less protection against infection to people taking ocrelizumab or fingolimod, who have an impaired immune response to vaccines, than the general population. These findings will have implications for vaccination policies.

7.2. Introduction

While real-world data in the general population continued to show that COVID-19 vaccination is effective in preventing infections,[2 3] it was unclear whether it offered the same level of protection to people with MS receiving

immunomodulatory DMTs. Immunological studies reported on humoral and cellular immune responses to COVID-19 vaccines among people on MS DMTs,[4-8] but they lacked findings on the effectiveness of vaccines in preventing infections in this population. It was important that monitoring the population effect of COVID-19 vaccination is inclusive of people on immunomodulatory treatments,[2] especially as COVID-19 restrictions were being relaxed.

The present study aimed to understand the impact of mass COVID-19 vaccination in preventing SARS-CoV-2 (symptomatic and asymptomatic) infections on the entire population of people taking MS DMTs in England.

7.3. Materials and Methods

This is a retrospective analysis of prospectively and longitudinally collected national data by the NHS England and NHS Improvement (NHSE/I) and the UK Health Security Agency (UKHSA).

7.3.1. Population Data

NHSE/I acquire prescribing data on all commissioned MS DMTs in England.[9] The total number of people on MS DMTs (including alemtuzumab, beta-interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, and teriflunomide) during each month from March 2020 to August 2021 was estimated based on their last DMT prescription any time before and including the last day of each month since January 2019.

The total population of England was captured from publicly available data.[10] The population of adults aged 20 years or above was used to match the MS population who over 98% of them are adults (The Multiple Sclerosis International Federation, 2020).[11]

7.3.2. SARS-CoV-2 Infection Data

UKHSA has collected data on all registered SARS-CoV-2 test results, including RT-PCR and rapid antigen tests (RAT; i.e., LFT), from the start of the pandemic which is publicly available for the general population.[12] The datasets of NHSE/I and UKHSA were merged to identify all people taking MS DMTs who tested positive for SARS-CoV-2 during each month from March 2020 to August 2021. The last prescribed MS DMT any time before the date of a positive test was used to determine the DMT a person with MS was taking when they tested positive.

The available data on SARS-CoV-2 infections for both people with MS and the general population included people with 1) positive RT-PCR, 2) positive RAT confirmed by positive RT-PCR taken within 72 hours, or 3) positive RAT when RT-PCR was not done within 72 hours (89.8%, 7.4%, and 2.8% of cases in the general population by the end of August 2021, respectively).[12] People with positive RAT but negative RT-PCR within 72 hours were not included as a case of SARS-CoV-2 infection. People with more than one positive test were counted once and the date of their first positive test was used.

7.3.3. Statistical Analysis

The incidence rate of SARS-CoV-2 infection was calculated for the general population and people on MS DMTs. The incidence rate ratio (IRR) was calculated as the incidence rate of SARS-CoV-2 infection among people taking MS DMTs divided by the incidence rate among the general population. The 95% CI was estimated using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

In England, mass SARS-CoV-2 vaccination started in December 2020 and COVID-19 restrictions were gradually lifted from March to July 2021. The IRR and 95% CI were calculated for each month during the study period as well as during two waves of the COVID-19 pandemic: (1) three months around the start time of mass SARS-CoV-2 vaccination (November 2020 to January 2021) referred to as pre-vaccination, and (2) three months after the start of mass vaccination (June to August 2021) referred to as post-vaccination.

7.4. Results

A mean (SD) of 41,208 (4,301) people with MS received DMTs in England during each month from March 2020 to August 2021. A total of 3,524 people taking MS DMTs had SARS-CoV-2 infection during this period.

The monthly incidence rate of SARS-CoV-2 infection among people on MS DMTs and the general population is presented in Figures 7.1 to 7.9 (the data are available online at https://ars.els-cdn.com/content/image/1-s2.0-S2211034821007240-mmc1.xlsx).

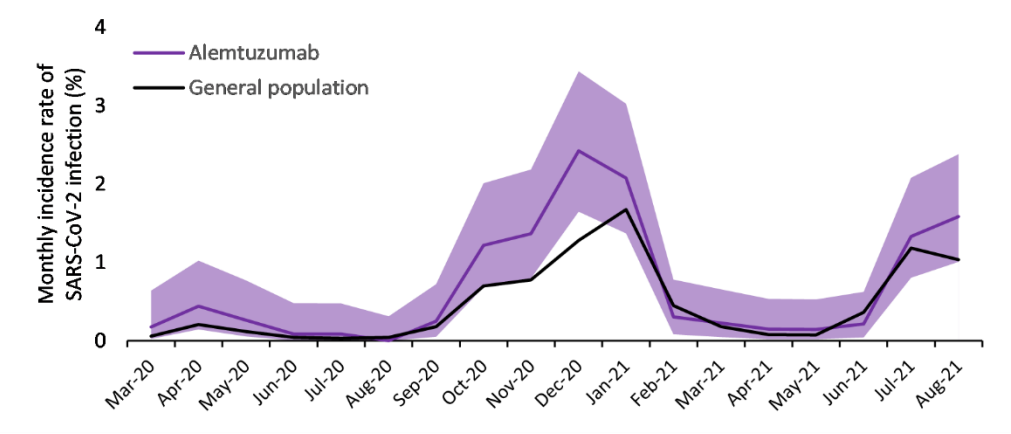

Figure 7.1. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving alemtuzumab versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking alemtuzumab, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

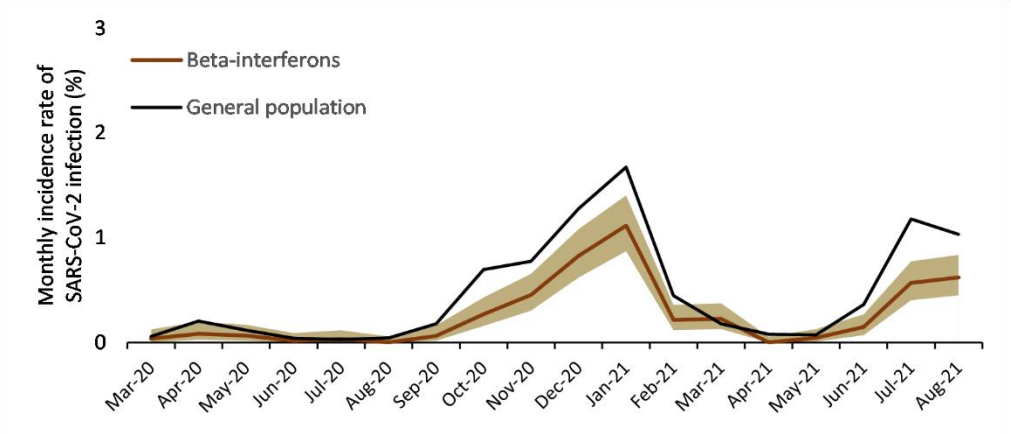

Figure 7.2. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving beta-interferons versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking beta-interferons, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

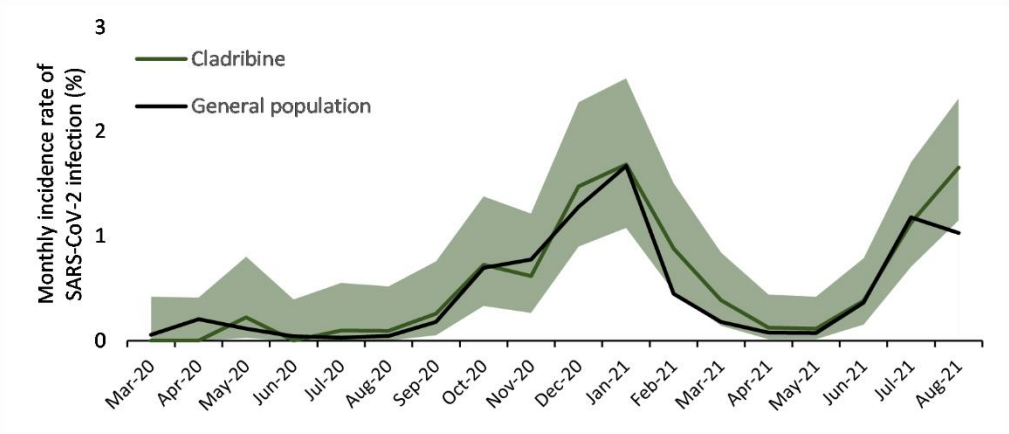

Figure 7.3. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving cladribine versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking cladribine, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

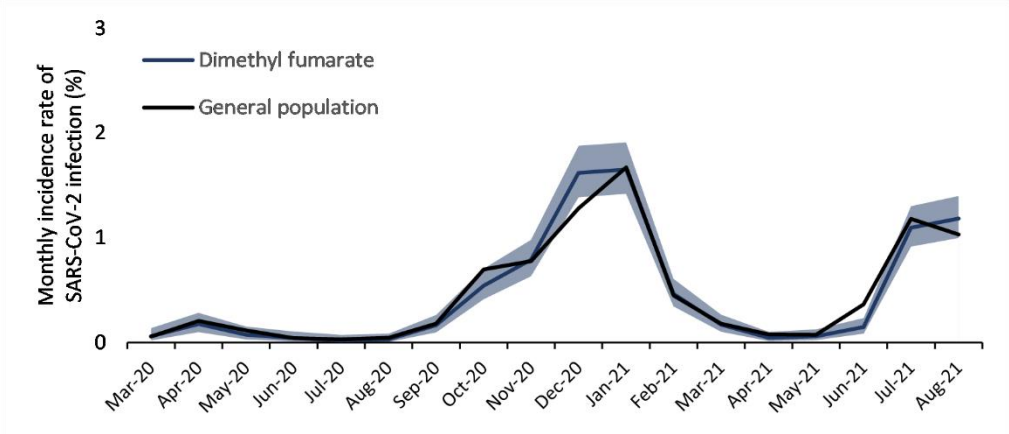

Figure 7.4. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving dimethyl fumarate versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking dimethyl fumarate, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

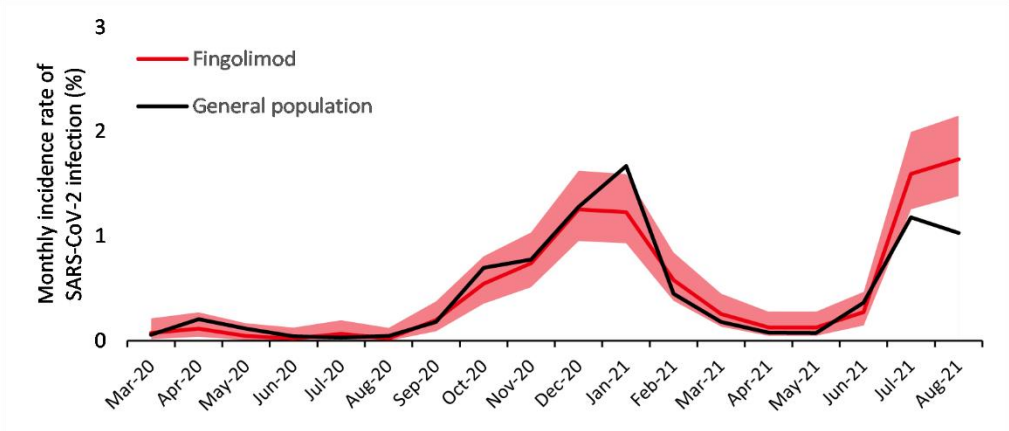

Figure 7.5. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving fingolimod versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking fingolimod, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

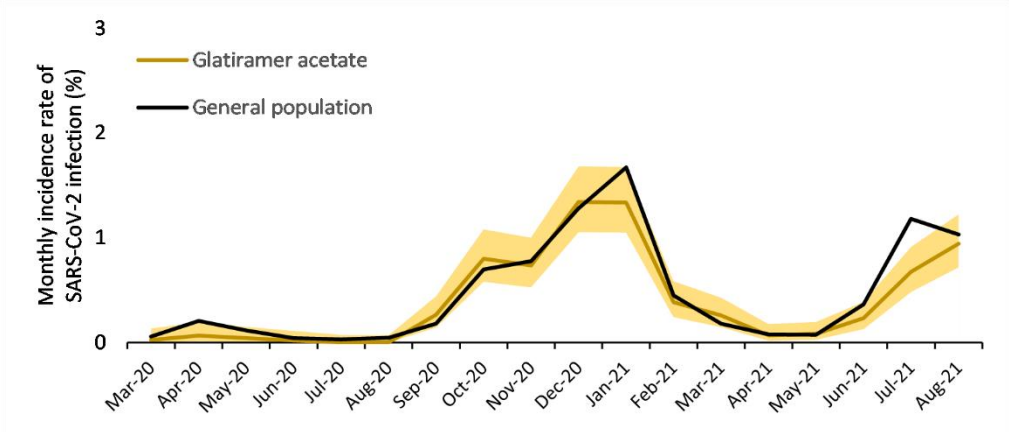

Figure 7.6. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving glatiramer acetate versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking glatiramer acetate, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

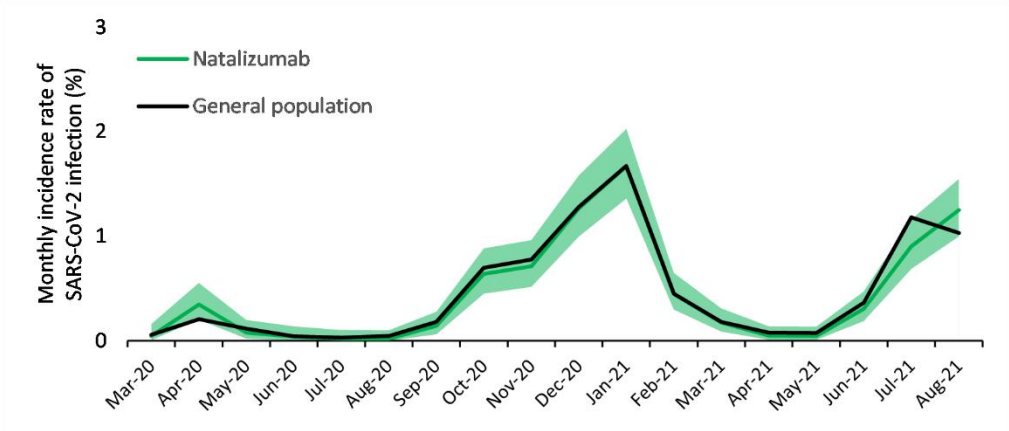

Figure 7.7. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving natalizumab versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking natalizumab, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

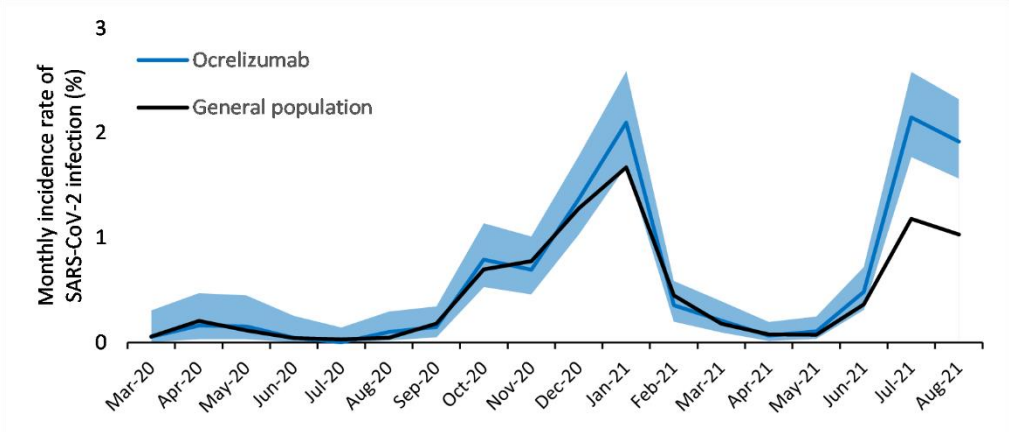

Figure 7.8. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving ocrelizumab versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking ocrelizumab, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

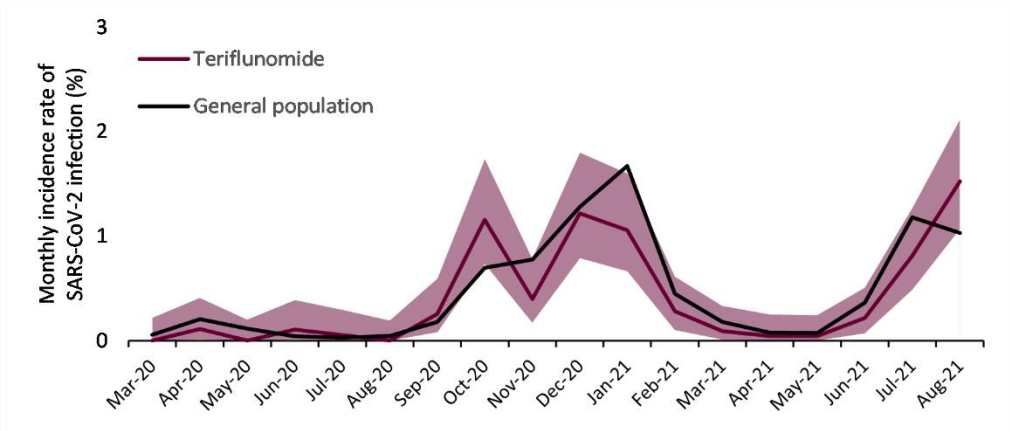

Figure 7.9. Monthly incidence rate of SARS-CoV-2 infection among people with MS receiving teriflunomide versus the general population of 20-years-old or above in England. The coloured line is the incidence rate of infection during each month per 100 people with MS taking teriflunomide, and the shaded area is the 95% confidence interval. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

The IRR (95% CI) of infection for people on ocrelizumab versus the general population significantly increased from 1.13 (0.97–1.31), pre-vaccination, to 1.79 (1.57–2.03), post-vaccination (Figure 7.10). For people on fingolimod, this also significantly increased from 0.87 (0.73–1.02) to 1.40 (1.20–1.63) (Figure 7.10). There were no significant changes for people on other MS DMTs (data are available online at https://ars.els-cdn.com/content/image/1-s2.0-S2211034821007240-mmc2.xlsx and https://ars.els-cdn.com/content/image/1-s2.0-S2211034821007240-mmc3.xlsx).

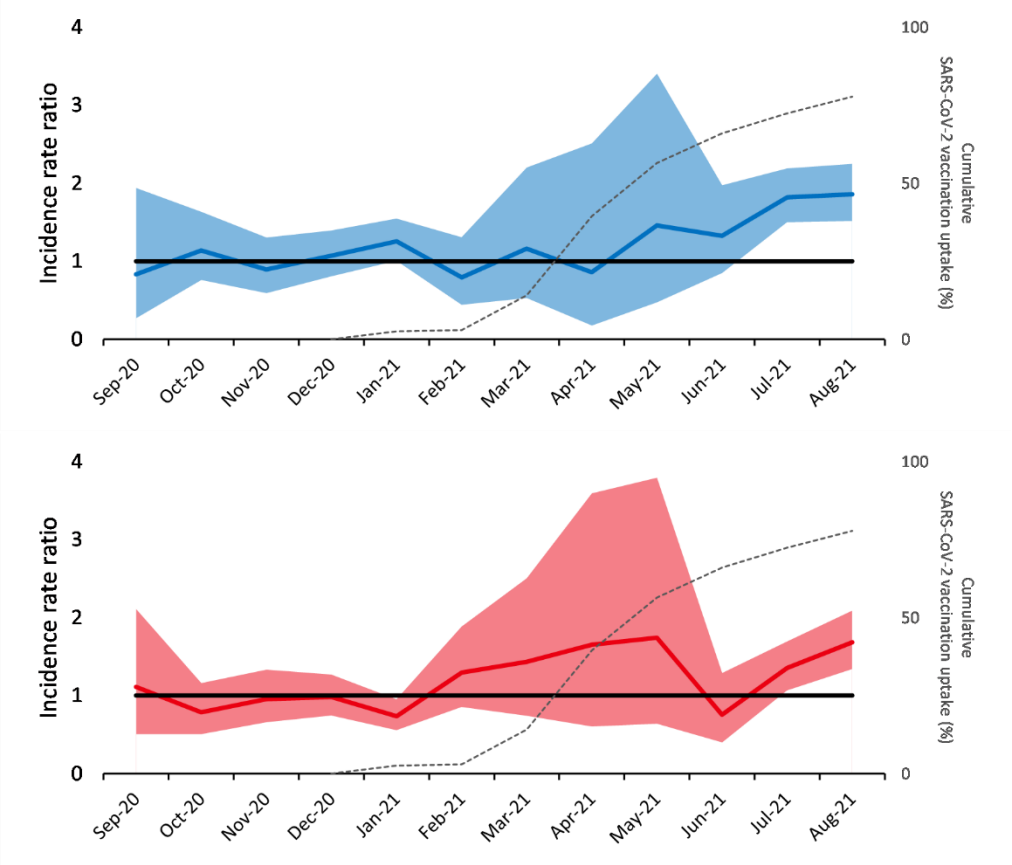

Figure 7.10. Incidence rate ratio of SARS-CoV-2 infection among people with MS taking ocrelizumab and fingolimod compared to the general population aged 20 years or above in England. Data for ocrelizumab (top) and fingolimod (bottom) are presented in separate graphs. The coloured line in each graph is the incidence rate ratio and the shaded area is the 95% confidence interval. The black line demarcates the incidence rate ratio in the general population which is always one and serves as a reference line. The dashed grey line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

7.5. Discussion

This study presents the incidence of SARS-CoV-2 infection for the entire population of people with MS receiving DMTs in England and compares their risk of infection to the general population before implementation of mass COVID-19 vaccination and when at least 74% and 56% of the adult population had received their first and second doses of the vaccine, respectively.[12] To our

knowledge, this is the first study to report changes in the risk of SARS-CoV-2 infection in relation to mass vaccination in a population under immunomodulatory therapies. Although individual-level data on COVID-19 vaccination was not available at the time of the study, the MS population were expected to have a similar pattern of vaccination to the general population as they had a high willingness to be vaccinated,[13] or may have been vaccinated earlier (people with severe neurological disabilities or those taking alemtuzumab or ocrelizumab).[14] The study used positive SARS-CoV-2 test results which includes both symptomatic and asymptomatic infections.

The findings of this study show a substantial increase in the risk of SARS-CoV-2 infection among people on ocrelizumab or fingolimod compared to the general population following the liberalisation of COVID-19 restrictions and despite mass vaccination. There were no obvious changes in the risk of infection among people taking other MS DMTs.

People on ocrelizumab and rituximab show reduced antibody and memory B-cell responses to COVID-19 vaccines.[4-8] Nevertheless, they can mount a T-cell response to these vaccines.[5-7] It is unknown how this interplay between humoral and cellular immune responses translate into protecting people on these anti-CD20 B-cell depleting therapies from infection. Fingolimod also seems to prevent the production of antibodies in response to COVID-19 vaccination.[4 8] So far, assumptions about the impact of MS DMTs on the effectiveness of COVID-19 vaccines are based on experiences with previous vaccinations and these immunological studies rather than population-based

studies.[4-6 8 15] Cohort studies to assess the effectiveness of COVID-19 vaccines in people taking MS DMTs have been set up, but it will be a while before they are concluded.[8] The findings of our study suggest that the humoral immune response to vaccines, which is suppressed by ocrelizumab and fingolimod and preserved by other MS DMTs,[4-6 8] may be mainly responsible for the protection provided against SARS-CoV-2 infection.

We also noted that the risk of SARS-CoV-2 infection associated with beta-interferons was lower than the general population, both pre- and post-vaccination, which is not unexpected given their antiviral effects.[16]

The effectiveness of COVID-19 vaccination in preventing symptomatic infections and severe disease among patients taking MS DMT is yet to be determined. The timing of vaccination in relation to administration of some MS DMTs, such as alemtuzumab, cladribine, and ocrelizumab, can affect the development of an immune response to vaccines,[15] which was not applied in the present study because of individual-level data not being available at the time of this study. Also, other potential confounders, such as age, sex, or place of residence, could not be considered in the analysis because of the same reason.

7.5.1. Conclusions

These preliminary findings suggest that COVID-19 vaccines offer minimal protection against infection to people taking ocrelizumab or fingolimod. Population studies using individual-level data on vaccination (including

interval between vaccination and SARS-CoV-2 infection), antibody levels, infections, and disease severity are required to establish the benefits of current vaccination programmes and offering third dose vaccines to people with drug-induced immunosuppression.

7.5.2. Up-to-date Literature Review

It is reassuring that COVID-19 vaccines can trigger an immune response in people with MS, including those on most DMTs, and are effective in preventing severe outcomes of the infection, such as hospitalisation and death, in this population.[17 18]

However, several immunological studies conclusively confirm that anti-CD20 monoclonal antibodies (mostly including ocrelizumab and rituximab) and sphingosine 1-phosphate receptor modulators (mostly including fingolimod) impair the humoral immune response to COVID-19 vaccines and significantly lower the rate of seroconversion in people with MS treated with these DMTs compared to healthy controls, untreated people with MS, and people with MS receiving other DMTs.[18] In addition, sphingosine 1-phospate receptor modulators suppress the cellular immune response to COVID-19 vaccines, an effect that has not been observed with anti-CD20 monoclonal antibodies.[18]

There is still a lack of robust clinical studies on the risk of contracting COVID-19 and its severe outcomes in vaccinated people with MS. A study, however, showed an association between breakthrough infections in people with MS receiving DMTs and low levels of humoral immune response to COVID-19

vaccines.[19] It is, therefore, possible that people with MS on ocrelizumab or fingolimod have a higher risk of COVID-19. Another study found that fully vaccinated people with MS receiving rituximab have a higher risk of hospitalisation due to COVID-19 compared to other DMTs.[20] Nonetheless, this risk significantly declined when COVID-19 vaccines were administered 6 months after the last infusion.[20] I continued my work on NHS England data to explore the rate of hospitalisation and death due to COVID-19 in the fully vaccinated MS population on DMTs and presented our preliminary findings at the 2022 annual meetings of the ABN and American Academy of Neurology (the presentation slides have been included in Appendix 7-B).[21 22] Given the need to further clean the data and confirm these findings, they have not been included as part of this thesis.

Overall, these studies are in line with the findings of the above NHS England study. Moreover, the NHS England study corroborates the results of the UKMSR study that people with MS were not at increased risk of contracting COVID-19 before the implementation of the COVID-19 vaccination programme (see Chapter 2).

Further studies on improving the immune response to COVID-19 vaccines (e.g., adjusting the timing, booster doses, etc.) in people with MS receiving anti-CD20 monoclonal antibodies and sphingosine 1-phosphate receptor modulators are required, especially as the use of these MS DMTs is rising. It seems that during periods of low COVID-19 transmission in the community (Figures 7.1. to 7.9), people with MS taking DMTs—including ocrelizumab and

fingolimod, were not at a significantly higher risk of contracting COVID-19 compared to the general population. This finding signifies the importance of preventing the spread of infection in the general community, in addition to taking actions specifically for the MS population.

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Chapter 8

Decentralised Clinical Trials in MS Research

8. Decentralised Clinical Trials in MS Research

The published article[1] is included in Appendix 8-A.

8.1. Abstract

Randomised controlled trials (RCTs) play an important role in MS research, ensuring that new interventions are safe and efficacious before their introduction into clinical practice. Trials have been evolving to improve the robustness of their designs and the efficiency of their conduct. Advances in digital and mobile technologies in recent years have facilitated this process and the first RCTs with decentralised elements became possible. Decentralised clinical trials (DCTs) are conducted remotely, enabling participation of a more heterogeneous population who can participate in research activities from different locations and at their convenience. DCTs also rely on digital and mobile technologies which allows for more flexible and frequent assessments. While hospitals quickly adapted to e-health and telehealth assessments during the COVID-19 pandemic, the conduct of conventional RCTs was profoundly disrupted. In this paper, we review the existing evidence and gaps in knowledge in the design and conduct of DCTs in MS.

8.2. Introduction

Randomised controlled trials (RCTs) are an essential component of modern healthcare, ensuring that new interventions are safe and efficacious before their introduction into clinical practice. RCTs, however, are expensive, time-

consuming and burdensome to participants, investigators and funders, highlighting a need for innovations that reduce their high 'failure' rate.[2-5] Success may be threatened, for example, by lack of funding due to prohibitively high costs,[2 4] low statistical power due to failure to recruit or retain participants,[4 6] or lack of generalisability due to being biased towards a certain population (e.g. towards individuals who are more able to attend in-person study visits).[4 7] Therefore, initiatives are being developed to optimise the efficiency of the conduct of RCTs; decentralised clinical trials (DCTs) being one of these innovations.[8-10]

DCTs are defined as trials in which different elements of the trial such as recruitment, delivery and administration of interventions, study visits, assessment of outcomes and data collection are executed remotely.[11 12] They obviate the need to travel to a trial centre for participants, and therefore, enable participation from different locations by people who may not have been able to participate in the trial otherwise.[11 12] DCTs frequently rely on digital and mobile technologies, allowing for more flexible assessments that are not bound by the limitations of scheduled on-site study visits.[11] A transition from conventional, centralised RCTs to DCTs was on the horizon prior to the COVID-19 pandemic,[8 9 11] but the demand for such evolution in the design and conduct of RCTs has been recognised more widely during the pandemic and some of their techniques have been rapidly adopted.[13-15]

RCTs play an important role in MS research as new DMTs and symptomatic treatments are still required. In this paper, we review the existing evidence and gaps in knowledge in designing and conducting DCTs in MS research.

After the parameters and scope of the review were agreed by the authors, PubMed and Google Scholar databases and the Google search engine were searched through July 2021 using the keywords (in different combinations) 'decentralised (or decentralized), randomised (or randomized) controlled trial (or clinical trial or trial), remote, digital, virtual, online, and electronic' and 'multiple sclerosis'. For each section, outlined in the review, additional keywords, corresponding to each topic, were used for a more targeted search. All relevant articles and the references cited in these articles were reviewed. If MS-specific articles for any of the sections were considered insufficient, a similar search was performed after excluding the keyword 'multiple sclerosis' to find relevant articles from other fields of neurology or medicine.

8.3. Conceptual Framework

To ensure that RCTs are appropriately powered for testing the efficacy of a treatment within a limited sample size, they are performed under controlled circumstances where participants tend to have homogeneous characteristics.[16] Therefore, the findings of RCTs are typically not generalisable, and trials of treatments in real-world populations and under usual clinical practice settings are required to test their effectiveness.[16-18] Trial designs are moving towards integrating efficacy and effectiveness studies to

save time and cost.[16] DCTs can help reduce this efficacy–effectiveness gap by enabling the conduct of pragmatic trials on a larger number of participants with more heterogeneous demographic and clinical characteristics from different locations and practice settings.[15 16]

RCTs also examine the efficiency of therapeutic interventions, that is, their cost-effectiveness.[19] There are benefits to undertaking such economic analysis as part of RCTs, such as using prospectively collected patient-level data rather than performing retrospective population studies, but there are also limitations,[19 20] which could be overcome through DCTs. Conventional RCTs may fail to take real-world costs of a treatment into account.[19 21] Since extensions of RCTs can be expensive and demanding for both investigators and participants, the follow-up duration of most conventional RCTs are often too short to collect patient-level data on long-term indirect costs of treatment,[19] such as costs of monitoring MS DMTs, switching MS DMTs or disruptions in their use, their side effects, disability progression due to MS, lost productivity, relapses and hospitalisations.[21] Also, the cost-effectiveness of an MS DMT estimated in a centralised RCT of a few centres may not be applicable to other healthcare settings due to their lack of generalisability.[19] Although DCTs cannot eliminate all these problems, they can improve estimations of cost-effectiveness by enabling incorporation of real-world data into RCTs, allowing for long-term follow-up, and increasing the generalisability of their findings.[22] The costs and savings of applying remote and digital techniques in administration and monitoring of interventions should be

carefully calculated when assessing the cost-effectiveness of a proposed treatment in a DCT.

8.4. Recruitment, Retention, and Study population

MS already imposes a high burden on patients by adversely affecting their health and productivity and demanding that a substantial proportion of their time is dedicated to their clinical care.[23 24] Participating in trials can further disrupt participants' daily routine and they may incur indirect costs, such as arranging a caregiver.[25 26] Difficulties of transport to the study site or having other commitments appear to be the main reasons for declining participation in, or withdrawal from, a study.[27 28] Therefore, RCTs commonly recruit participants at a slower rate than planned or lose participants to follow-up.[6 29 30] Insufficient recruitment and retention can lead to delays in trial completion, additional costs, underpowered and biased results or premature trial termination.[25 29 31 32] The same issues can also lead to the inadvertent exclusion of some people with disabilities, multiple comorbidities, or caring or job responsibilities, or people who live far away from, often urban, study sites,[4 33] and reduce the generalisability of the findings.[7]

DCTs can improve participation in studies and retention of participants by allowing them to engage in research activities without the need to travel to a study site and to undertake these activities at their convenience based on their personal and daily schedule.[11 33 34] For example, people who are unable to walk may be excluded from conventional RCTs, and their participation can

be facilitated through DCTs. Therefore, DCTs can include a more diverse group of participants, improving the trial's generalisability and reducing bias.[35] For example, MS patients managed in community health services and those managed in specialist MS clinics can be different populations. The findings of a conventional RCT, which tends to recruit participants from MS clinics and hospital settings, may not be generalisable to the broader MS population.[36] DCTs can be leveraged to enrich recruitment by targeting these underrepresented populations in conventional RCTs. Larger study populations may, however, be required because of the heterogeneous study population and increased variability in outcomes,[37 38] but this may be a reasonable trade-off for improving the external validity of a trial. The growing use of electronic health records will also facilitate confirmation of diagnosis and review of eligibility criteria during recruitment.

There is a risk that people who prefer in-person interactions or are unable to use digital technologies – for example, due to technological illiteracy, physical disabilities, cognitive or visual problems or lack of resources to support the use of such technologies (e.g., high-speed Internet connections), may still be excluded from DCTs.[39 40] Advancements in technologies may enhance the usability of digital tools for certain populations. In some circumstances, willing friends or family members could be trained to assist participants with completion of their trial activities remotely. Trials may need to consider more complex hybrid designs, which provide both remote and on-site options, to

ensure that their study population is representative of the real-world patient population.

MS trials of therapeutic interventions rarely require the identification of participants in inpatient settings. However, RCTs of some acute inpatient treatments, for example, management of severe disabling relapses, will inevitably require recruitment of participants within inpatient settings with remote follow-up, hence, adopting a hybrid approach to RCTs. Moreover, trials that involve imaging outcome measures are more likely to require hybrid designs.

8.5. Study Visits

The growing use of telehealth and e-health tools in routine care of people with MS facilitates the shift towards remote study visits in RCTs.[41 42] For example, these tools are already being used for providing information regarding a study and remote consenting, including real-time interaction between potential participants and the research staff to ensure that an informed decision is made.[43 44] The digitisation of other components of a study visit will be reviewed in the following sections.

8.6. Outcome Measures

8.6.1. Clinical

The prospect of digitising outcome measures has played a role in envisaging a future where DCTs are practical.[45] We report on how digital technologies can

reshape RCTs but the specifics of each digitised outcome measure are beyond the scope of this review.

Several existing outcome measures are being or have been converted into tele- or digital assessments to enable remote monitoring of participants and providing them with flexibility in timing their research activities (e.g. the Expanded Disability Status Scale or the Multiple Sclerosis Functional Composite).[40 45 46] This approach allows for more frequent and even continuous assessments (as opposed to infrequent in-person study visits that tend to be restricted by time), leading to increased power of a study.

People with MS commonly experience fluctuations in their physical and cognitive performance, sometimes exacerbated by the fatigue associated with travel to study sites, which can affect the findings of a trial depending on participants' performance capacity at the time of testing.[39 47] Repeated measurements can, therefore, be more realistic and closer to participants' natural performance compared to cross-sectional assessments.[39 47] Monitoring composite outcomes in real-time allows for a more dynamic analysis that accounts for the potential relationship between different health-related outcomes,[48] for example, the effects of participants' fatigue, pain or mood on their mobility. Real-time recording of patient-reported outcomes not only prevents recall bias, which is likely to occur with retrospective reporting during study visits, but also enables the integration of subjective perceptions of symptoms and objective measurements (e.g., detecting fever during a presumed MS relapse).[49] E-health and telehealth technologies can

improve reporting MS relapses or adverse events in a DCT. The ease and frequency of evaluations in a DCT may, however, lead to over-reporting of side effects compared to conventional RCTs.[45]

Furthermore, the emerging digital evolution in the provision of healthcare presents an opportunity to use routinely collected clinical data in DCTs.[45] Linking electronic health records to electronic records of RCTs will enable the use of real-world data and outcomes, such as hospital admissions and potential adverse events, which might, otherwise, go unreported.[50]

The digital era has also unlocked opportunities to develop new outcome measures or to assess additional aspects of participants' performance when using existing ones.[39 40] Portable and wearable devices, such as smartphones and smartwatches, enable measurement of participants' physical activity through both passive monitoring and active instructed tests,[29 40 49] and their use appears to be acceptable to people with MS.[29] These technologies not only capture conventional measures of physical disability in MS, such as mobility or dexterity, but also introduce objective measurements of other aspects of physical health, such as falls, fatigue, sleep and autonomic dysfunction, which commonly affect the quality of life of people with MS but can be invisible or difficult to capture in conventional RCTs.[40 49] The application of wearable sensors, however, goes beyond the quantification of physical and physiological features and is also being considered for measuring biomarkers in bodily fluids.[51] Digital tools also allow the assessment of participants' learning curves during repeated tests (e.g. Trail Making Tests A

and B, Ishihara test, n-back task and 9-Hole Peg test) to evaluate their ability to learn a task and their response speed in addition to response accuracy.[39]

Digital tools and their remote application will require standardisation and validation before their introduction into RCTs,[14 52] which is being addressed by a growing number of MS-specific studies in recent years.[40 49] Although the outlook for using digital outcome measures is promising, they can still overburden participants with excessive and complex tasks.[33] Research staff often directly oversee the completion of outcome measures during in-person study visits, which improves compliance. While data collection could be negatively affected due to poor compliance of participants when they are asked to report outcome measures remotely, routine checks for compliance (e.g., automated emails that go out if an outcome measure is not completed, followed by personnel contact at the next level) can be built into the structure of DCTs to prevent it. Research staff may need to spend more time following up on missing or invalid data with remote compared to on-site data collection. So, it remains possible that the convenience of DCTs will be offset by the inconvenience of the process of remote data validation.

8.6.2. Imaging

Magnetic resonance imaging (MRI) is one of the most widely used tools in RCTs of MS DMTs.[52] The use of MRI in a trial may limit decentralisation as participants need to travel to a study site to undergo scans. Mobile and community-based MRI scanners are available,[53] and can improve participants'

access. Developing and implementing standardised MRI protocols across sites, enabling participants to be scanned at the closest centre, is a practical solution.[54] The use of standardised MRI protocols for MS diagnosis and follow-up is being advanced by international MS associations.[54] They are developing strategies to overcome its challenges, such as scanner differences or engagement of different MRI centres, which can also be employed in MS research.

8.7. Therapeutic Interventions

Currently, most RCTs of therapeutic interventions in MS that are conducted remotely involve rehabilitation or psychotherapy.[40] To the best of our knowledge, there are no entirely remote RCTs of pharmacological interventions in MS; our search within clinical trial registries (clinicaltrials.gov and the ISRCTN registry) did not reveal any such studies. Although the remote administration and monitoring of rehabilitation or psychotherapy is facilitated through readily available e-health or telehealth technologies, which are currently being used,[40 41 55] this is not yet applicable to pharmacological interventions such as DMTs. Pharmacies are increasingly providing drug delivery services to patients' homes,[56] but the delivery and administration of some investigational medicinal products can be difficult to undertake entirely remotely; they may require specialised handling during delivery (e.g. cold chain management) or close monitoring during administration.[11]

The administration of some treatments, such as drug infusions, must be monitored by healthcare providers, but could be conducted in home settings. Some local healthcare providers already offer these services to people with MS and can be utilised in DCTs involving altered administration of established DMTs (e.g. extended interval dosing of natalizumab).[57] Home visits are an alternative approach (e.g. cardiac monitoring at fingolimod initiation or home administration of steroids for relapses);[58 59] however, the application of these methods to improve participants' access to trials of investigational medicinal products will require the establishment of dedicated local or mobile research centres.

Digital technologies can be employed for remote monitoring of medication usage and measuring adherence. Direct monitoring of participants' adherence to a medication by the research staff can be laborious and expensive, and reporting of drug usage by participants can be unreliable.[60] Digital tools, such as electronic needle disposal systems, electronic pill bottles or electronic diaries enable objective and real-time monitoring of medication usage,[40] which along with electronic drug reminders can improve adherence.[40 60]

8.8. Data Protection

It is evident that the General Data Protection Regulation and other data privacy regulations will also apply to DCTs, but additional considerations regarding data safety and security during their collection, transfer, handling,

use and storage will be required for these trials.[11 61] While the specifics of these regulations are beyond the scope of this review, some examples include policies for using passive data, linking multiple sources of data and ensuring data security on mobile technologies as well as during their transfer in the complicated process of data flow in DCTs.[61 62]

Although digital technologies, through strategies discussed above, present an opportunity to reduce missing data in an RCT, clear instructions on data management need to be included in study protocols to avoid data loss.[11 61]

8.9. Ethics

Institutional Review Boards (IRBs) may be unfamiliar with some approaches that are used in DCTs and have not been widely implemented in trials. As a result, the ethical and regulatory review process for a DCT may be prolonged compared to a conventional RCT. Regulatory bodies and researchers need to work closely with IRBs to ensure that DCTs meet all the criteria for ethical research.

8.10. Study Sites and Setup

It is likely that as centralised RCTs evolve into DCTs, the organisation of study sites will transform as well. Local clinical trial hubs and mobile facilities run by a network of clinical research employees could still perform research activities that cannot currently be done remotely (e.g., MRI scans, sample collections and drug administration). Remote conduct of RCTs can facilitate more widespread involvement of smaller study sites in trials.[14]

Remote study site initiation and staff training has commonly been used during the COVID-19 pandemic, and might be preferred, because it saves time and cost.[63] It is important to ensure that the research staff are trained appropriately for their roles in a DCT, which will entail different responsibilities compared to a conventional RCT (e.g. management of electronic, instead of manual data entries or training participants to use digital tools).[14]

Digital tools should be made user-friendly and run efficiently so that the research staff are not overburdened by tackling technical problems.[33] Implementing a technical core or help centre into the structure of DCTs may alleviate the pressure on research staff.

8.11. Costs

RCTs are expensive and digitising them is thought to reduce their cost.[64] A 2011 study showed that decentralised trials have higher data management costs than centralised trials.[65] Although reduced in-person study visits in DCTs will save costs, the added costs of the remote approaches discussed above are study specific. It is likely that advancements in digital technologies (e.g., unified rather than local data storage) and their more widespread use will reduce these costs. Also, the reduced risk of delays in trial completion or its failure is probably an economic advantage of DCTs over conventional RCTs. The evidence regarding the costs of DCTs compared to conventional RCTs is

limited, however, and may change over time with developments in DCT designs and their widespread application.

8.12. Implementation

The aim of implementation research is to narrow the gap between finding an efficacious and effective intervention and its evidence-based use in clinical practice.[66] Implementation strategies are increasingly being explored within trials to accelerate this process.[66] DCTs will involve remote and potentially novel modes of administering and monitoring treatments that might have not been introduced into routine care. DCTs could demonstrate the feasibility of certain remote processes that could be adopted to introduce efficiencies in clinical practice. Considering implementation issues at early stages of a DCT is vital to ensure that the intervention can be delivered in clinical practice and to identify adaptations required to achieve the same level of effectiveness.

8.13. Conclusion

Clinical trial designs continue to evolve with the aim of improving efficiency and robustness. Advancements in digital and mobile technologies in recent years have facilitated this process and initiated what we think is a gradual transformation from centralised to decentralised RCTs. DCTs have the potential to increase the statistical power of RCTs, produce more generalisable and less biased results and run more efficiently compared to conventional RCTs by recruiting large heterogeneous study samples, more frequent assessments of outcome measures, capturing participants' real-

world performance and timely trial completion. Organisations have started projects to develop and improve the design and conduct of DCTs.[8-11]

DCTs, however, may not be applicable in all circumstances and, therefore, hybrid approaches are also likely to be implemented. Full transition to DCTs may not be immediately possible as some methods discussed in this review need further validation before their widespread application in trials. However, these are times of great opportunities to adjust and improve clinical trials to better serve our patients.

8.14. References

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Chapter 9

Conclusion

9. Conclusion

In this chapter, I will describe the impact of my research, as part of the wider MS and COVID-19 research ecosystem that was built during the COVID-19 pandemic, on different aspects of the health care of people with MS. It will also thematically summarise the work of this thesis and present directions for future MS care and research.

9.1. Impact Statement

A purpose of my MS and COVID-19 research was to empower people with MS in a period of uncertainty by involving them in shaping the research and keeping them informed about the evolving implications of the COVID-19 pandemic for them. People with MS, including lay people and academics with MS, were involved in all stages of this work and their perspectives formed most of the research questions. I have presented and discussed our findings at multiple meetings with people with MS to create a mutual conversation around this research. I have worked closely with the MS Society to communicate our findings to people with MS and support them, with information, during the COVID-19 pandemic.

From the early days of the COVID-19 pandemic, the findings of this work were used to formulate the guidelines of the ABN for the use of MS DMTs.[1] This research was advocated by the ABN, who recognised its importance and potential contribution in a time when there was little to no information on the interplay between COVID-19 and MS.[1] The collective

global MS and COVID-19 research played a major role in policymaking decisions for people with MS during and following the COVID-19 pandemic. In the UK, people who were receiving anti-CD20 monoclonal antibodies (i.e., ocrelizumab, rituximab, and ofatumumab) and alemtuzumab became one of the priority groups to receive primary and booster doses of the COVID-19 vaccines.[2] People with MS—irrespective of their DMT status, became eligible to receive anti-COVID-19 treatments in 2022.[3] This advice was modified in 2023 to include only people with MS on immunosuppressive therapies.[4] I believe that our research contributed to COVID-19 and MS research becoming an example of timely translation of good quality research—given the disruption of clinical and research activities and the fast-evolving nature of the COVID-19 pandemic, into practice, which can take years otherwise.[5]

9.2. COVID-19 in People with MS

In Chapter 2, I discuss that, before COVID-19 vaccines became available, people were not at increased risk of contracting COVID-19 because they had MS, had physical disabilities due to MS, or were using any of the MS DMTs.[6 7] In fact, they shared the same risk factors as the general population for contracting COVID-19 (e.g., ethnic minorities).[8 9] However, when a person with MS got COVID-19, they were more likely to be adversely affected if they had higher levels of neurological impairment, were on anti-CD20 monoclonal antibodies, or had recently received corticosteroids.[10] As I present in Chapter 4, people with MS seem to take longer to recover from COVID-19 than the

general population, and their recovery can be prolonged even further if they have more physical disability, have pre-existing anxiety and/or depression, or are female.[11] MS DMTs do not affect COVID-19 recovery time in a community-based population of people with MS and COVID-19.[11] These factors need to be considered in the long-term rehabilitation of people with MS and COVID-19. These findings also highlight the importance of preventing COVID-19 in the MS population.

In Chapter 7, I show that, despite the success of COVID-19 vaccines among the general population and people using other MS DMTs, people on ocrelizumab and fingolimod were at a disadvantage due to their lack of immune response to these vaccines and were at higher risk of contracting the infection.[12-14] It has yet to be confirmed whether people on ocrelizumab and fingolimod have a higher risk of severe COVID-19 outcomes despite vaccination. Further research is needed to investigate ways to mitigate the lack of immune response to vaccines in this large and growing population of people with MS on anti-CD20 monoclonal antibodies and sphingosine 1-phosphate receptor modulators (e.g., adjusting the timing of vaccine and DMT administration).

9.3. COVID-19 and MS Disease Course

In Chapter 3, I report that COVID-19 can cause new MS symptoms or exacerbate pre-existing ones around the time of infection.[15] Interestingly, MS DMTs seem to prevent the occurrence of these new MS symptoms following

COVID-19, suggesting that they may prevent CPVID-19-related relapses.[15] These findings indicate that a holistic approach, considering all the risk and benefits of MS DMTs, is needed before deciding to alter the choice or administration of DMTs due to a fear of infection. Other studies have shown that COVID-19 does not affect the clinical or radiological disease activity of MS that is independent of infection, which is reassuring.[16 17]

9.4. COVID-19 and Mental Health in MS

In Chapter 5, my findings add to the extensive evidence that people with MS are more likely to have anxiety and depression than the general population—with or without a global health crisis such as the COVID-19 pandemic.[18 19] I also demonstrate that poor mental health—which tends to be chronic, has a substantial negative effect on MS symptoms and general health in this population, which is almost twice the negative—and acute, effect of COVID-19.[18] Although these findings seem intuitive and are not exclusive to the period of the COVID-19 pandemic, health and social care resources are not designed in a way to fully support people with MS and mental health problems.[20] Moreover, contrary to the early perception that 'COVID-19 does not discriminate', I found that COVID-19 does discriminate indeed, which is in line with other research focusing on ethnicity and socioeconomic factors.[18] The lifestyle, social relationships, and employment of people with MS were more adversely affected by the pandemic than the general population.[18]

9.5. MS Research

In this thesis, I have used two large-scale databases to study the impact of the COVID-19 pandemic on people with MS: 1) the UK MS Register, a prospective and longitudinal community-based cohort of people with MS in the UK that has been collecting data on a wide range of fields from 2011, and 2) the NHS England database (provided by the Arden and GEM Commissioning Support Unit), a database that had not been explored for MS clinical research prior to this work and includes prescribing and dispensing data on all MS DMTs in England. This research is an example of how the COVID-19 pandemic shaped a global response within the MS community, using available resources or creating new ones, to conduct and implement good quality and timely research in MS and COVID-19.[21]

The COVID-19 pandemic altered research activities with implications for future research.[22-24] In Chapter 8, I review the current literature on decentralised clinical trials in MS research, a novel approach to clinical trials that became even more relevant with the changes imposed by the COVID-19 pandemic on research.[25]

9.6. Summary

In this thesis, I tried to address the impact of the COVID-19 pandemic on different aspects of the lives of people with MS. I have presented the extent to which the MS population was affected by this infection, before and after the roll-out of the COVID-19 vaccination programme. I have reported the MS-

specific factors that influence the chances of contracting COVID-19 in this population. I have depicted the interplay between COVID-19 and MS—i.e., how people with MS recover from COVID-19 and how COVID-19 affects their MS symptoms. I have examined the mental health status of the MS population and its determinants covering a period from before to during the COVID-19 pandemic. I have stated the implications of these findings for MS care and discussed areas for future research. I have ended this thesis by reviewing the literature on decentralised clinical trials, which was inspired by the impact of the COVID-19 pandemic on all research, including the present work.

9.7. References

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Appendix 1-A

University of Nottingham
UK | CHINA | MALAYSIA

First Year Report for Confirmation Review

Doctor of Philosophy (PhD)

in

Clinical Neurology

Report from October 2019 to August 2020

Supervisors

Prof. Cris Constantinescu

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Division of Clinical Neurosciences

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Abbreviations and Acronyms

bFFE	balanced Fast Field Echo
BMI	Body Mass Index
BSA	Body Surface Area
CNS	Central Nervous System
CoV	Coefficient of Variance
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSA	Cross-Sectional Area
CSF	Cerebrospinal Fluid
DM	Diabetes Mellitus
DN4	Neuropathic Pain 4 Questions
DPN	Diabetic Polyneuropathy
D-QoL	Diabetes Quality of Life
EDSS	Expanded Disability Status Scale
FLAIR	Fluid Attenuated Inversion Recovery
FMRIB	Oxford Centre for Functional MRI of the Brain
FSL	FMRIB Software Library
GAD-7	Generalized Anxiety Disorder-7

HADS	Hospital Anxiety and Depression Scale
HSMN	Hereditary Sensory Motor Neuropathy
ICV	Intracranial volume
IES-R	Impact of Event Scale-Revised
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
LOT-R	Revised Life Orientation Test
MNSI	Michigan Neuropathy Screening Instrument
MPRAGE	Magnetization sequences Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale 29
NCS	Nerve Conduction Studies
NPS	Neuropathic Pain Scale (NPS)
PAID	Problem Areas in Diabetes
PHQ-9	Patient Health Questionnaire-9
PPMS	Primary Progressive Multiple Sclerosis
pwMS	people with Multiple Sclerosis
ROI	Region of Interest
RRMS	Relapsing-Remitting Multiple Sclerosis

RT-PCR	Reverse Transcriptase-Polymerase Chain Reaction
SARS	Severe Acute Respiratory Distress Syndrome
SCT	Spinal Cord Toolbox
SCS	Spinal Cord Stimulation
SD	Standard Deviation
SEP	Somatosensory Evoked Potentials
SPMIC	Sir Peter Mansfield Imaging Centre
SPMS	Secondary Progressive Multiple Sclerosis
T	Tesla
VAS	Visual Analogue Scale
webEDSS	web-based Expanded Disability Status Scale

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Background

I started working on a research project titled "Spinal Imaging in Neuropathy of Diabetes: Longitudinal Evaluation (SpINDLE)" when I commenced my postgraduate research course for a PhD in Clinical Neurology. We had recruited 6 participants before the COVID-19 pandemic hit the UK and affected our research activities. At the beginning, when people with significant comorbidities were advised to stay at home, we could not recruit participants into the study's disease groups, since most of these participants were of old age and had diabetes or multiple sclerosis and, therefore, were considered high risk. Then, with closure of the Sir Peter Mansfield Imaging Centre of the University of Nottingham- where the study scans took place, and with the primary outcome of the study being magnetic resonance imaging-based quantification of the spinal cord, we could not recruit healthy volunteer either. Also, shortly after, all non-essential research activities, including our study, were required to pause. Until today, the circumstances have remained the same. I have carried on with literature review and educating myself on spinal cord magnetic resonance imaging analysis during this period.

Moreover, I have managed to continue my research activities through engaging with another research project in COVID-19 and multiple sclerosis. At the early stages of the COVID-19 outbreak, we launched a national prospective longitudinal cohort study as part of the UK Multiple Sclerosis Register. In this unique research project, we are actively monitoring the impact of COVID-19 on a large population of people with MS in the UK from different clinical, psychological, and social aspects. So far, the study has resulted in several oral presentations in virtual national and

international meetings, including a presentation by myself on 3 June 2020 at the International Women in Multiple Sclerosis Global Scientific Meeting on the preliminary findings of the study. We also had a poster presentation at the 6th Congress of European Academy of Neurology and have submitted abstracts for presentation at this year's joint American and European Committee for Treatment and Research in Multiple Sclerosis meeting. In addition, we have submitted two papers for publication and are awaiting peer review. This research project is ongoing, and we are developing and disseminating new questionnaires to respond to the evolving nature of the COVID-19 pandemic. We hope that the findings of our study will eventually benefit the management of people with multiple sclerosis during these unprecedented times.

Chapter 1

Spinal Imaging in Neuropathy of Diabetes:

Longitudinal Evaluation (SpINDLE)

1. INTRODUCTION

1-1. Diabetic Polyneuropathy and the Importance of Its Early Detection

The International Diabetes Federation estimated the global prevalence of diabetes among adults at 9.3% in 2019. This growing pandemic of diabetes is expected to reach 578 million people worldwide by 2030.[1] Also, Diabetes UK reported that currently, about 4.7 million people have diabetes in the UK which will exceed 5.5 million in a decade.[2] With this increase, the already high number of patients with chronic complications of diabetes will rise even further.[3]

Diabetic neuropathies are the most common chronic complications of both type 1 and type 2 diabetes and account for most cases of neuropathy worldwide.[4 5] Diabetic neuropathies have a broad spectrum of clinical presentations, and they can affect any type of peripheral nerve fibres (sensory vs motor vs autonomic) at various sites (focal vs multifocal vs generalised) with different patterns of nerve injury (axonal vs demyelinating) and disease course (acute vs chronic).[4-6]

Diabetic polyneuropathy (DPN) is the most prevalent form of all neuropathies in diabetes and accounts for approximately 75% of the cases.[6 7] DPN is clinically defined as a symmetrical length-dependent generalised neuropathy affecting both sensory and motor nerve fibres in the peripheral nervous system (PNS).[5 8] The prevalence of DPN increases with the duration of diabetes[7 9] with nearly half of diabetic patients developing DPN during their lifetime.[6 7]

Foot ulcers, painful neuropathy, and falls are the main clinical consequences of DPN[5 10 11] which have a negative impact on the health of patients and economies.[12-18] Since none of the existing treatments can reverse the natural course of DPN,[19 20]

clinical or research interventions to prevent the progression of DPN and its sequelae must be employed at earlier stages of the disease before irreversible nerve damage has occurred.[20-23] This timely diagnosis of DPN requires screening strategies that can detect it before overt clinical signs and symptoms of neuropathy develop.[5 6 20 23] Also, we are currently relying on clinical and neurophysiological (i.e., nerve conduction study [NCS]) findings to assess the severity of DPN which are not accurate enough to monitor the progression of neuropathy over time.[24-28]

1-2. Evidence of Spinal Cord Involvement in Diabetic Polyneuropathy

DPN is primarily known as a disorder of the PNS. However, there is mounting evidence that the central nervous system (CNS), including the spinal cord, is also involved in DPN, [29 30] with references to a co-existing 'diabetic myelopathy' being made in the literature throughout the last century or so.[31 32]

This section will discuss the evidence around spinal cord involvement in DPN.

1-2-1. Pathology

Almost all pathological studies of the spinal cord in DPN date back to the late 19th and 20th century. The most frequent pathological finding was found to be degeneration of the dorsal columns of the spinal cord with evidence of demyelination, axonal loss, and fibrosis.[33-35] Nevertheless, the spinal cord also displayed a diffuse and symmetrical pattern of degenerative changes that affect both the sensory and motor pathways.[35] Diabetic vascular changes of the spinal cord, on the contrary, were mostly focal and generally did not correlate with the extent of nerve damage, leading to the conclusion that spinal cord degeneration in DPN probably takes place independent of an angiopathic process.[34 35] Moreover,

lesions of the peripheral nerves and nerve roots appeared more pronounced compared to the corresponding spinal cord tracts. Therefore, it was assumed that spinal cord changes in DPN result from retrograde degeneration of the peripheral nerve fibres.[35] The metabolic disturbances associated with diabetes were also considered to have a role in spinal cord pathology in DPN.[32 34]

It is not clear whether the described pathological findings in the spinal cord can be attributed to DPN alone. In an era where diabetes management was not optimal, almost all studied patients showed evidence of DPN, making it difficult to decide whether spinal cord changes occur in all diabetic patients or solely in those with DPN.[34 35] Given that disorders such as subacute combined degeneration and tabes dorsalis, which also mainly affect the dorsal columns, could not be accurately diagnosed during this period, it is probable that some of the spinal cord changes seen in DPN were secondary to these conditions rather than diabetes.[33 36]

1-2-2. Spinal somatosensory evoked potentials

Electrical stimulation of a peripheral nerve generates impulses that ascend through the somatosensory pathway. As these discharges travel through different parts of the PNS and CNS, they create electrical potentials that can be captured by placing recording electrodes at certain locations across this pathway. It is then possible to calculate the conduction time of these somatosensory evoked potentials (SEP) between recording sites using.[37]

A few SEP studies have found prolonged conduction times in the spinal cord of patients with DPN,[38-40] while others have failed to demonstrate such delays.[41] To add to these discrepancies, a study has shown slowing of spinal conduction in

diabetic patients with little or no evidence of DPN.[42] It appears that even when the conduction velocity of the spinal cord decreases, the reduction does not correlate well with that of the peripheral nerves in patients with DPN.[39 43] This observation refutes the hypothesis that retrograde axonal degeneration of the peripheral nerves is the only cause of spinal changes in DPN.[39 43]

Altogether, without a head-to-head comparison of spinal cord conduction in diabetic patients with or without DPN, it is impossible to conclude, based on SEP, whether spinal changes in DPN are concomitant to or independent of the peripheral neuropathic process.

1-2-3. Spinal cord stimulation

Spinal cord stimulation (SCS) has been used for the treatment of pharmacologically intractable chronic pain since 1967.[44] The electrical stimulation applied to the epidural space of the spinal cord in this technique inhibits the transmission of nociceptive signals from the PNS to the brain.[44]

Several studies have shown that SCS offers sufficient and sustained pain relief in many cases of painful DPN refractory to medical therapy.[45-51] Two of these studies also examined the severity of DPN among SCS responders and non-responders in the short-term, and could not detect any significant differences between the two groups. [49 51] However, a more recent study with five years of follow-up shows that patients with more severe degrees of DPN have an almost four-fold higher risk of long-term treatment failure with SCS.[52] This finding matches the early observation in 1996 that DPN patients with severe loss of vibration and position senses do not

respond to SCS.[45] It is speculated that patients with severe DPN fail to respond to SCS because of injury to spinal cord pathways.[45 52]

1-2-4. Spinal cord magnetic resonance imaging

In a pilot study, a group of researchers showed that the lower cervical (C4−C5) and upper thoracic (T3−T4) cord cross-sectional areas (CSA) were lower in patients with DPN compared to controls without diabetes.[53 54] They could not, however, make the same observation in comparison to diabetic patients without DPN or about the lower thoracic (T9−T10) cord.[53 54] Later, in a larger cross-sectional study, the same researchers, using the same measurement techniques, found that the upper cervical (C2−C3) cord CSA in patients with clinical DPN is lower than controls without diabetes (17%), diabetic patients without DPN (15%), or patients with hereditary sensory-motor neuropathies (HSMN) that do not involve the spinal cord (20%).[55] They found similar findings in patients with subclinical DPN (i.e., patients without clinical manifestations of DPN but with evidence of neuropathy on NCS).[55] The researchers also demonstrated that patients with clinical DPN have a lower upper cervical CSA compared to those with subclinical DPN.[55] However, the cervical CSA was similar in diabetic patients without DPN and controls (Figure 1).[55]

The finding that shrinking of the spinal cord begins early on in DPN− even before clinical signs and symptoms develop, in addition to the absence of spinal cord atrophy in diabetic patients who do not have DPN suggest that spinal cord area can serve as a marker for early detection of DPN in diabetic patients. Moreover, the reduction in spinal cord area as the neuropathy advances from subclinical to clinical indicates a potential for its use in monitoring the progression of DPN. However,

further longitudinal studies are required to confirm these observations and to assess the rate of atrophy as a starting point to reforming our approach to early diagnosis and monitoring of DPN.

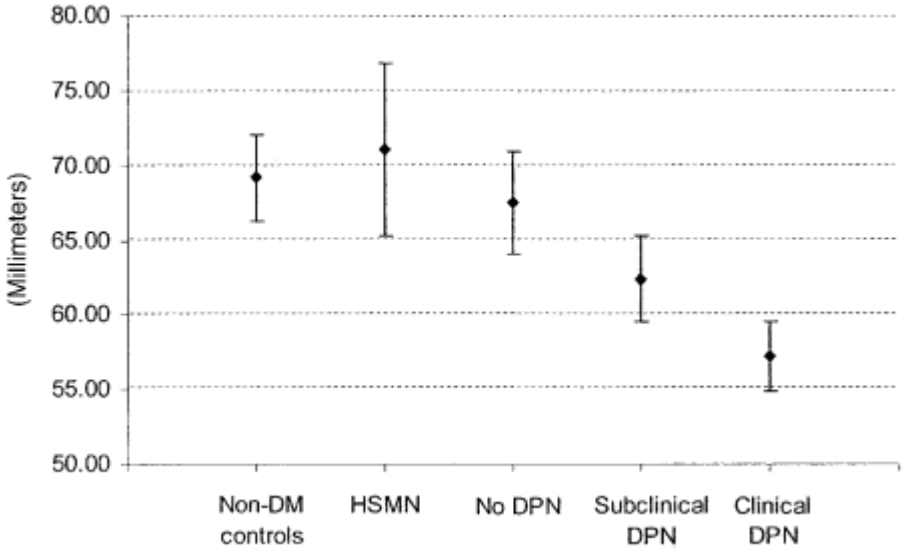

Figure 1. Mean and 95% confidence interval of normalized upper cervical cord CSA per group (copied from "Early involvement of the spinal cord in diabetic peripheral neuropathy" by D Selvarajah et al, 2006, Diabetes care, 29(12):2664-69)

1-3. Quantification of Spinal Cord Atrophy Using Magnetic Resonance Imaging

Spinal cord atrophy is a feature of many neurological diseases and MRI has provided an avenue to examine it quantitatively in-vivo. Various techniques have been developed to measure the spinal cord using MRI. However, a consensus has yet to be reached as to which method is most accurate and reliable. The issue mainly stems from 1) the inability to acquire simultaneous ex-vivo measurements of the spinal cord to compare to its MRI-based estimations, and 2) the need to control for multiple factors, including MRI metrics, during scans to reduce inter-subject and intra-subject variability of images.

Spinal cord atrophy has been explored as an imaging biomarker in many different conditions involving the spinal cord, such as inflammatory, degenerative, and traumatic disorders of the nervous system,[56-58] and, so far, the literature in multiple sclerosis (MS) and related diseases has exceeded others which also include the work of the researchers at our department at the University of Nottingham.[59 60]

Quantification of the spinal cord using MRI began with manual measurements of the cord diameters,[61] and later, manual outlining of the spinal cord to calculate its CSA. Manual methods were time-consuming and had poor reproducibility; hence, the development of semi-automatic and automatic methods.[62] These MRI-based procedures generally rely on calculating either the cord CSA or its volume, with the majority of studies reporting the former.[63 64]

This section discusses the considerations for MRI-based measurements of the spinal cord and the strengths and limitations of different techniques.

1-3-1. Site of spinal cord cross-sectional area measurement

The CSA of a spinal cord segment (e.g., C2−C3) is estimated by calculating the mean CSA of all axial MRI slices at that segment. Similarly, the CSA of a spinal cord region (e.g., upper cervical) is the average of the CSA of all corresponding segments. The decision as to which segments to use for measuring the CSA depends on the spinal cord level affected in any given disorder as well as the MRI appearance of the cord at different levels.

For accurate measurement of the CSA, the spinal cord needs to be clearly delineated on an MRI. In order to achieve this, the cerebrospinal fluid (CSF) should surround all aspects of the spinal cord on the image to create a high anatomic

contrast (as seen in figure 3.a). Moreover, the spinal cord should appear straight in the segments that are being evaluated for CSA. Otherwise, the transverse cross-section of the spinal cord would not lie perpendicular to the cord long axis, leading to overestimation of the CSA (Figure 2). Most methods have evolved to correct for this spinal orientation throughout their calculations by estimating the angle of the spinal cord long axis compared to the imaging axis.[65 66] It is also important to measure the CSA at a level in which anatomic landmarks can be easily identified so that the CSA is measured at the same level, from one scan to another (in a single individual or among many individuals), during studies. The spinal cord CSA is usually measured using a limited number of segments which helps to minimize scanning duration and, therefore, reduce the chance of motion artefacts because of subjects becoming tired or restless.[67] The quality of images on cervical MRI are least affected by movement.[68]

The upper cervical cord not only possesses all the above characteristics for efficient image acquisition and segmentation but is also the main site of pathology in MS, the ground on which most quantitative methods of spinal cord atrophy evaluation have been developed.[63 67] There is also evidence that the upper cervical cord is involved in DPN,[55] making it a relevant site to study spinal cord atrophy.

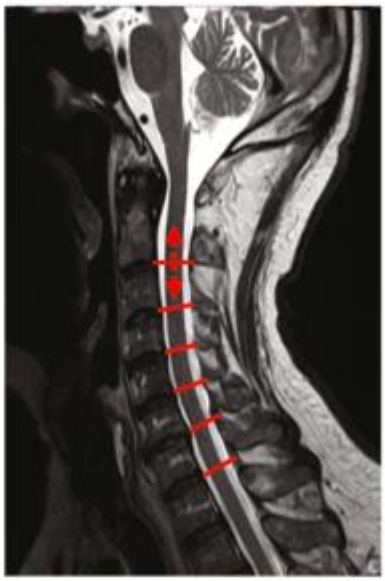

Figure 2. The actual cross-section of the spinal cord (red lines) at the C2-C3 segment is perpendicular to the axial plane, but the cross-section deviates further from the axial plane as it moves towards the thoracic cord (image adapted from “Segmental differences of cervical spinal cord motion: advancing from confounders to a diagnostic tool” by M Hupp et al, 2019, Scientific reports, 15;9(1):1-9)

1-3-2. Intensity-based methods: spinal cord edge detection

The spinal cord cross-section at its largest segment, C5, is estimated to have a mean (± 2 standard deviations [SD]) transverse diameter (i.e., along the coronal plane) of 13.3 ± 2.2 mm and an anteroposterior diameter (i.e., along the sagittal plane) of 7.4 ± 1.6 mm,[69] which gives an approximate cross-sectional area of 77.3 mm^2 and circumference of 33.2 mm. A typical voxel in a high-resolution structural MRI is 1 × 1 × 1 mm. If all voxels at the edge of the spinal cord only consisted of cord tissue, the area covered by these edge voxels would be about 43% of the cervical CSA and even higher in smaller spinal cord segments. However, the voxels of the spinal cord edge on axial MRI slices include partial volumes of both the cord itself and the surrounding CSF. Therefore, including edge voxels in measurements of the spinal

cord or excluding them from the measurements can result in significant overestimation or underestimation of the CSA, respectively.[62 65] It is important, therefore, that in the quantification of the spinal cord CSA, the contaminated voxels in the spinal cord edge are taken into consideration.

A simplistic approach is to hypothesize that the spinal cord and CSF contribute equally to the edge voxels and exclude one-half of the edge voxels when calculating the CSA.[65] Another approach is to estimate the amount of each edge voxel's contribution to the spinal cord CSA, giving a measurement that is closer to the actual CSA.[65] NeuRoi[70] is an image analysis software developed at the University of Nottingham which uses the latter approach.[65 67] In this program, the fraction of spinal cord tissue in each edge voxel (ƒ) is calculated using the MRI signal intensities of the spinal cord, CSF, and each edge voxel from the equation

$$I_{edge} = ƒ \times I_{cord} + (1 - ƒ) \times I_{CSF},$$

where I_{edge} is the intensity of a spinal cord edge voxel, I_{cord} is the intensity of the spinal cord, and I_{CSF} is the intensity of the CSF.[65] Each voxel within the spinal cord boundary contributes one voxel area to the total CSA and each edge voxel contributes a fraction (i.e., ƒ) of one voxel area to the total CSA. For this purpose, NeuRoi uses a semi-automated technique to detect all edge voxels and consists of the Sobel operator and nonmaximal suppression. Each voxel has an intensity gradient (G_i) which, simply put, signifies the direction and amount of change in their intensity and is measured using the Sobel operator. Each voxel, in a two-dimensional (2D) axial MRI slice, has an intensity gradient along the x-axis (G_x) and one along the y-axis (G_y). Therefore, the G_i vector is calculated from the equation

$G_i = G_x \hat{x} + G_y \hat{y}$,

where $\hat{x}$ and $\hat{y}$ are the directions of the vector in the x-y plane. Once the G_i for all voxels has been calculated, it is assumed that any voxel with the maximal $|G_i|$ compared to their two adjacent voxels (i.e., those closest to being in the directions of G_i and $-G_i$ from the voxel) is an edge voxel. As its name implies, nonmaximal suppression delineates the image edges by keeping the voxels with maximal $|G_i|$ and suppressing the rest (Figure 3.b). To automatically form the region of interest (ROI), which, here, is the spinal cord cross-section, NeuRoi requires manual identification of the spinal cord. The operator will place a seed point on the spinal cord and the software will expand it to include all spinal cord voxels up to and including the edge voxels, which have previously been identified (Figure 3.c).[65]

Conventionally, NeuRoi uses the 3D MPRAGE (three-dimensional magnetization sequences prepared rapid acquisition gradient echo) sequence,[65 67] which has an optimized T1-contrast and signal-to-noise ratio.[71] However, the procedure in NeuRoi can be applied to any MRI sequence.[70]

In summary, NeuRoi uses an intensity-based method to detect the spinal cord edge and is superior to former intensity-based methods because of partial volume averaging of the edge voxels.[62]

Figure 3. a) Axial image of the cervical cord surrounded by CSF. b) Edges automatically detected by the Sobel operator and nonmaximal suppression. c) The cord-CSF edge voxels form a region of interest around the cord (copied from "Measurement of cervical spinal cord cross-sectional area by MRI using edge detection and partial volume correction" by CR Tench et al, 2005, Journal of Magnetic Resonance Imaging, 21(3):197-203)

1-3-3. Surface-based methods

1-3-3-1. Active surface model

Another image analysis software, Xinapse JIM,[72] uses the active surface model to measure the spinal cord CSA.[66] It can create a 3D model of the spinal cord surface, making measurements of both spinal cord CSA and volume possible. The centre of the spinal cord is marked manually on different axial MRI slices at regular intervals. These marked centres serve as the initial point of several radius vectors for automatically generating a surface on cross-sections of the spinal cord (Figure 4 and Figure 5.A). On each axial image, an intensity gradient vector at different locations along each one of the radius vectors is created. Xinapse JIM also uses the Sobel operator to calculate the intensity gradient of voxels. Then, mathematical computations are used to calculate the radius update force at each location. In simple words, the calculated force determines both the direction and the length at which each predefined radius vector should shift to update the surface; the radius will be pulled towards locations where the intensity gradient vector has the same orientation as the radius vector and pushed away from locations where the intensity

gradient and radius vectors have opposite orientations (Figure 5). In a T1-weighted MRI sequence as depicted in figure 5, the intensity gradient vector of a location in the spinal cord is away from the centre and that of a location in the CSF is towards the centre. The software will apply the same computations and procedures for each updated radius vector until none of the vectors move by more than the 0.1% of the initial radius vector value. Finally, based on the spinal cord surface that has been detected, the centre of the spinal cord will be automatically updated to calculate the surface area of the spinal cord cross-section. Xinpase JIM can be applied to both T1-weighted and T2-weighted MRI sequences.[66]

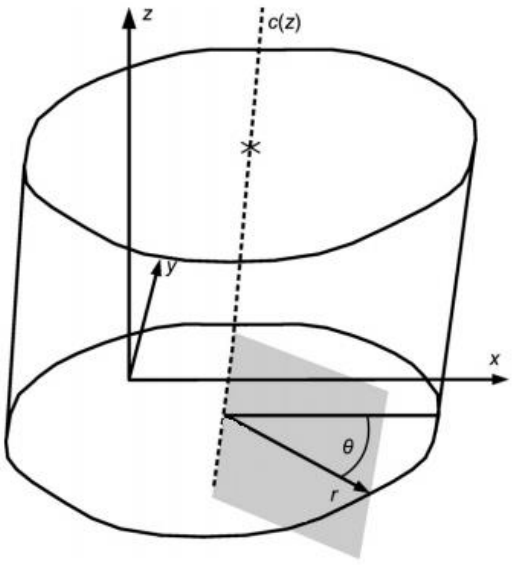

Figure 4. The centre line (c) is generated by connecting centre points marked by an operator on axial MRI slices. A radius vector (r) with a constant value is used to generate an initial surface as seen in Figure 5.A (adapted from “Rapid semi-automatic segmentation of the spinal cord from magnetic resonance images: application in multiple sclerosis” by MA Horsfield et al, 2010, Neuroimage, 50(2):446-55)

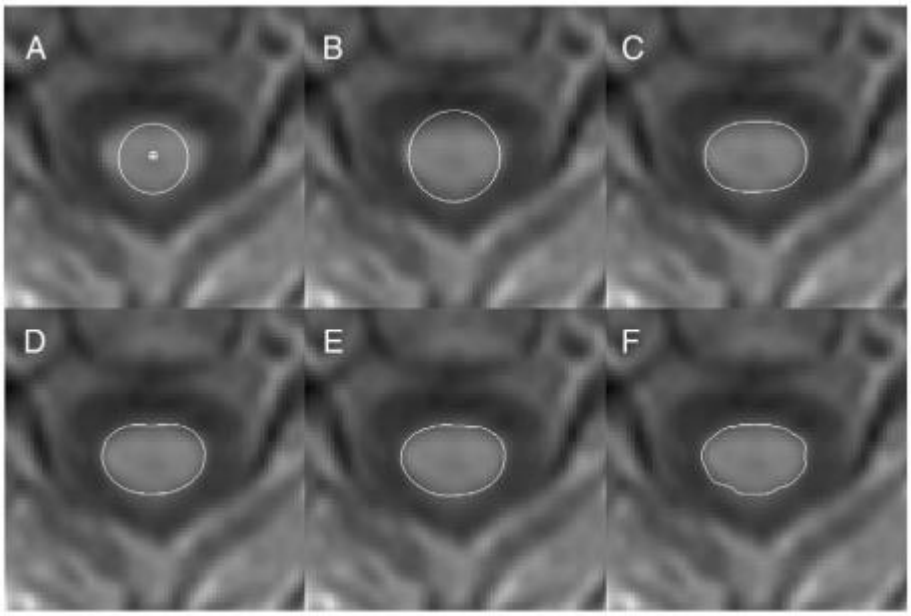

Figure 5. Evolution of the cervical cord active surface from A to F (copied from“Rapid semi-automatic segmentation of the spinal cord from magnetic resonance images: application in multiple sclerosis” by MA Horsfield et al, 2010, Neuroimage, 50(2):446-55)

1-3-3-2. Deformable model

PropSeg is another surface-based method to measure the spinal cord CSA as well as its volume,[62] and is part of a software for processing spinal cord MRI scans, the Spinal Cord Toolbox (SCT).[73] This approach provides a fully automated quantification of the spinal cord.

In SCT-PropSeg, the initial step of image analysis is automatic spinal cord detection.[73 74] The program selects an axial MRI slice. Based on the symmetry of the human body (i.e., mutual MRI data on the right- and left-hand sides of the axial image) computes a sagittal plane that passes through the spinal cord (Figure 6.1).[74 75] Then, on the axial image, a restricted region in the right-left direction from the sagittal plane is cropped, creating a restrained image (Figure 6.2). In the restrained image, circular and oval shapes are automatically detected by applying complicated

mathematical formulas which use the direction of intensity change at the edge and centre of a potential object to detect it (Hough Transform in figure 6.2). To identify the spinal cord among other objects that have a circular or oval cross-section (e.g., spinal canal or large blood vessels), the software, cleverly, selects the single object that is encircled by another (i.e., the spinal cord surrounded by the spinal canal as seen in figure 6.2).[74 75] It also take the proximity of the spinal cord to the sagittal plane into account when identifying the spinal cord.[74] The same procedure is applied to a few axial slices rostral and caudal to the original image, and the marked spinal cord structures on each axial slice are connected to confirm the approximate position and orientation of the spinal cord (Neighbourhood Analysis in figure 6.3).[74 75] To further validate the correctness of spinal cord detection, another series of computations are performed based on the contrast between the spinal cord and CSF intensities, the distance from the centre of the detected spinal cord to its edge, and the standard deviation of these distances (Discriminant Validation in figure 6.4).[74 75]

The next step for SCT-PropSeg is to build a tubular mesh inside the spinal cord based on the approximate position and orientation of the spinal cord that was previously determined (Figure 7).[74 75] Similar to Xinpase JIM, SCT-PropSeg uses the intensity gradient vectors to deform the tubular mesh and propagate it towards the spinal cord edge; hence, its name, the deformable model (Figure 7).[74 75]

Following the 3D delineation of the spinal cord, SCT-PropSeg identifies the spinal cord centre line and uses it as a guide to detect changes in intensity along the vertebral column. Sudden changes in intensity occur between the vertebrae and

intervertebral discs, providing the software with valuable data to locate the intervertebral discs and use them in the automatic calculation of the spinal cord CSA or volume.[74]

Another program called DeepSeg is also incorporated into SCT and uses a deep learning structure to train a convolutional neural network for spinal cord segmentation.[76]

Both SCT-PropSeg and SCT-DeepSeg can be applied to T1-weighted, T2-weighted and T2*-weighted sequences. It seems that the CSA measurements made by SCT at the same spinal level for T1- and T2-weighted sequences can be different which can be explained by differences in their image properties.[75] However, with optimized MRI protocols, all sequences show similar inter- and intra-scanner reliability when measuring the CSA.[77]

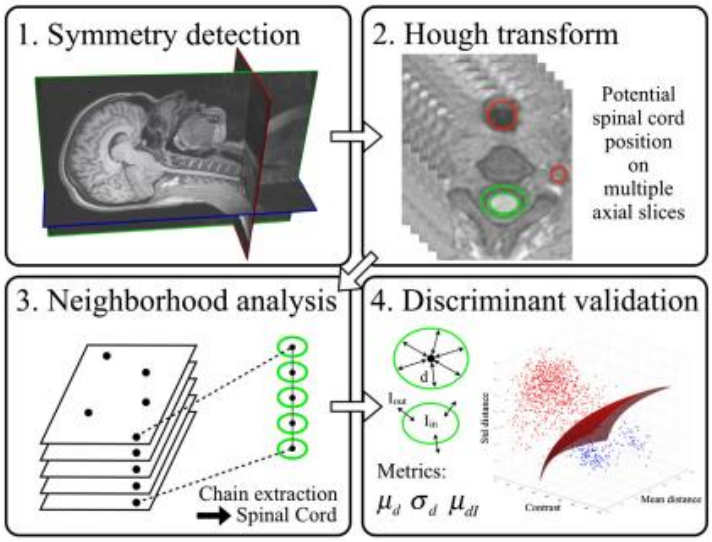

Figure 6. Spinal cord detection by SCT (copied from "Robust,accurate and fast automatic segmentation of the spinal cord" by B De Leener B et al, 2014, Neuroimage, 98:528-36)

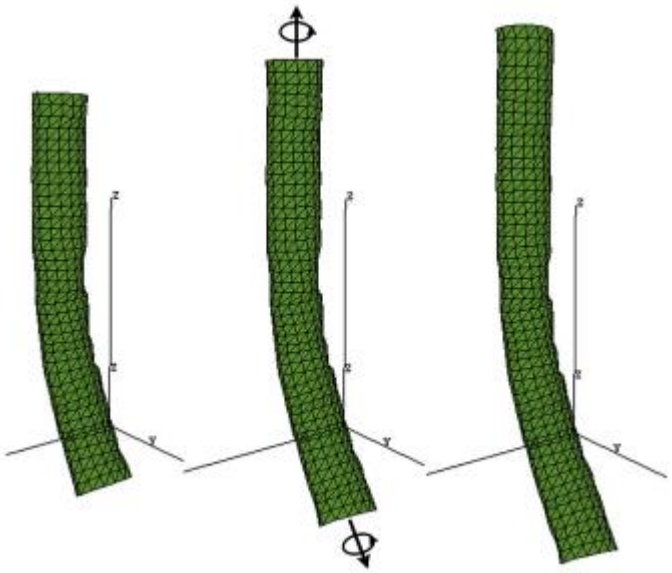

Figure 7. Propagation of the deformable model from left to right (adapted from "Robust,accurate and fast automatic segmentation of the spinal cord" by B De Leener B et al, 2014, Neuroimage, 98:528-36)

1-3-4. Correction for spinal cord orientation

As mentioned previously, to achieve an accurate measurement of the CSA, the spinal cord needs to lie perpendicular to the axial plane at each slice. An operator can position the axial axis of each segment perpendicular to the spinal cord during scanning which will generate slices that are closer to the natural cross-section of the spinal cord. However, relying entirely on an operator to acquire such images can be subjective and would allow for potential errors.[65]

NeuRoi overcomes this problem by estimating the angle (θ) between the plane of the axial image and the axial plane of the spinal cord and then, correcting for the increase in the CSA due to such inclination; it is expected that the CSA increases by 1/cos(θ). To estimate θ, NeuRoi identifies the centre of the spinal cord on each axial slice, and then, fits all the centres on a straight line.[65]

In Xinapse JIM and SCT, where a 3D surface of the spinal cord is generated, the CSA is calculated in a plane to which the spinal cord centre line is perpendicular.[66 75]

1-3-5. Strengths and limitations of models

1-3-5-1. Accuracy

Active surface and deformable models provide only an approximation of the spinal cord CSA since they use a limited number of points (i.e., the radius vectors or the mesh) to trace the surface. Edge detection models have the advantage of linear delineation of the spinal cord and including all voxels at the edge in CSA calculations. Furthermore, NeuRoi uses partial volume averaging of the edge voxels for accurate measurement of the spinal cord CSA.[62 65] Active surface and deformable models do not take this factor into account.[62]

When compared to the actual CSA of a phantom, the measurements made by NeuRoi tend to overestimate the CSA by only 3.15%.[65] However, active surface models have been shown to overestimate the CSA by between 4.3% to 10.8% when compared to a phantom.[78] Such comparisons to a phantom have not been made for SCT.[62]

Studies comparing the accuracy of SCT and Xinpase JIM against manual outlining of the spinal cord have shown contradicting results.[74 75 79] In two studies, SCT-PropSeg generally demonstrated a better accuracy on T2-weighted sequences and a better or similar accuracy on T1-weighted sequences compared to Xinapse JIM.[74 75] Another study compared the CSA on T1-weighted images, once between the two methods and once, separately, to manual segmentation of the spinal cord.[79] The mean upper cervical CSA of both methods were significantly lower than the manual

method (33%, 32%, and 6% lower for SCT-PropSeg, SCT-DeepSeg, and Xinapse JIM, respectively), and the measurements made by SCT were significantly lower than Xinapse JIM.[79] In other words, when compared against manual outlining of the spinal cord, there was significantly less similarity in the measurements made by SCT compared to that of Xinapse JIM.[79] A potential explanation for this discrepancy is that all studies have used manual segmentation of the spinal cord as a gold standard, while this method is subject to a high rate of inter- and intra-observer variability.[62]

Combining surface-based and edge detection models described above would potentially yield even more accurate measures of the spinal cord CSA,[65] but, to our knowledge, none of the available software are currently implementing this approach.

1-3-5-2. Reliability

The coefficient of variance (CoV) for NeuRoi when repeating measurements of CSA on different scans of the same individual (scan-rescan error) is 0.55%, and the CoV when performing the measurements repeatedly on the same scan (within-scan error) is 0.14%.[65] The intra-observer CoV for NeuRoi is estimated at 0.42%.[59] For Xinpase JIM, the intra-observer CoV is reported as 0.44% and the inter-observer CoV as 1.07%.[66] While both NeuRoi and Xinapse JIM seem to produce reliable results, there are no comparative studies between the two programs.

The reproducibility of CSA calculations in terms of scanning and rescanning have been assessed for SCT-PropSeg, SCT-DeepSeg, and Xinapse JIM in one study as presented in Table 1.[79]

Table 1. Reproducibility of cervical cord cross-sectional area measurements by SCT-Propseg, SCT-Deepseg, and Xinapse JIM within different MRI scanners.

MRI Scanner	CoV* (%)		
	SCT-PropSeg	SCT-DeepSeg	Xinapse JIM
GE	1.20	1.38	1.00
Philips	1.10	1.86	1.11
Toshiba	1.15	1.64	0.88
Abbreviations: MRI = Magnetic Resonance Imaging; CoV = Coefficient of variance * Represents the scan-rescan error within each MRI scanner			

1-3-5-3. Longitudinal studies

The described errors can yield variable measurements of the spinal cord CSA or volume which is a concern, especially when calculating the change in these measurements in an individual over time. Moreover, in longitudinal studies, different slices at slightly different regions of the spinal cord might be used to make such measurements at each separate scan which can cause inconsistencies. Recently, a method has been developed that uses Boundary Shift Integral to directly measure the change in the spinal cord of an individual over time.[80] This technique aligns the spinal cord from two different scans together and then, calculates the area of the spinal cord that does not overlap.[80] Despite being freely available,[80 81] clear instructions as to how to use the software have not been made available yet.[81]

As in cross-sectional studies of spinal cord atrophy, the technical variability of MRI scanning should be reduced as much as possible in longitudinal studies to allow for

the accurate evaluation of the rate of spinal cord atrophy, which, especially over short periods, can be small.[82]

1-3-6. Normalisation of spinal cord measurements

Inter-subject and intra-subject variability of MRI-based measurements, even in the absence of spinal cord pathology, form the basis for normalisation of these measurements.[83] Normalisation improves the power of studies that compare cord CSA or volume between groups (e.g., between people with a certain disease and healthy controls) by adjusting for the differences seen in the CSA or volume that are caused by variations in phenotype or scanning technique, rather than the disease itself.[83 84] However, the optimal approach for normalisation has yet to be identified. So far, normalisation of the cord CSA or volume has been investigated using the intracranial volume (ICV) or its CSA at different levels,[59 85 86] brain volume,[83] thecal sac volume,[85] spinal cord length,[84] lumbar cord enlargement area,[86] the height or diameter of vertebral bodies,[83] the spinal canal area or diameter,[83] head size,[83] body mass index (BMI),[84] or body surface area (BSA).[84] Among these, the spinal canal area and head size appear to be most useful for normalisation of cervical cord CSA.[83]

However, as explained above, MRI scanning protocols should be kept consistent so that inter-subject and intra-subject variations caused by scanning techniques is reduced and raw (without normalisation) measurements of the spinal cord can be used as well.[82]

1-4. Spinal Cord Atrophy in Multiple Sclerosis

As stated previously, almost all techniques for MRI-based evaluation of spinal cord atrophy have evolved around MS. As a result, various aspects of spinal cord atrophy in MS have been clarified to an extent that the Magnetic Resonance Imaging in MS group has recently recommended its implementation in the management of people with MS.[87]

MS is an immune-mediated inflammatory disorder of the CNS which leads to demyelination, neuro-axonal loss, and gliosis.[88 89] All these pathological changes, as well as the loss of synapses, contribute to shrinkage of the spinal cord in MS, which can also be detected on MRI.[89] Post-mortem pathological studies on people with MS of long duration, have confirmed the presence of spinal cord atrophy which is more pronounced in the cervical and thoracic regions of the cord.[90 91]

Depending on their disease course, people with MS can present with different phenotypes including relapsing-remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).[92] Cross-sectional studies that have used MRI to quantify the spinal cord CSA indicate that people with any type of MS have some degree of cervical spinal cord atrophy compared to those without the disease.[63 87 93] Also, people with progressive MS demonstrate a more profound reduction of CSA compared to those with RRMS.[63 94] A pooled analysis of these studies has found an approximate 10% loss of cervical CSA in people with MS compared to controls.[63] This difference is nearly 14% in people with progressive MS (i.e., PPMS and SPMS) and is closer to that reported by post-mortem pathological studies (20%).[63 91] This discrepancy can be explained, in part, by the nature of the latter studies which are more likely to include people who have died of more severe

forms of MS with longer disease durations. As opposed to pathological studies, MRI-based quantification of the spinal cord has the advantage of evaluating the CSA over time. Pooled analysis of such longitudinal studies has found a rate of 1.78% per year reduction in the cervical CSA in people with MS.[63]

Clinically, the spinal cord is one of the main sites of pathology in MS whereas DPN is not expected to substantially involve the spinal cord. It is, therefore, surprising that the estimated rate of spinal cord atrophy in DPN compared to controls without the disease has been reported 17% as opposed to 10% to 14% in MS.[55 63] However, the findings in DPN are based on a single cross-sectional study.[55] Also, disease duration can affect spinal cord atrophy in both DPN and MS. Therefore, head-to-head comparative studies of the spinal cord CSA in DPN and MS are required before drawing any conclusions.

2. HYPOTHESIS AND AIMS

In this observational study, we hypothesize that spinal cord atrophy in patients with DPN progresses over time. To test this hypothesis, we intend to determine the longitudinal course of changes in the spinal cord CSA in patients with DPN by comparing it to that of negative control groups (including people without neither diabetes nor polyneuropathy, patients with diabetes but without polyneuropathy, and patients with non-diabetic polyneuropathies that are not expected to involve the CNS) as well as patients with MS as a positive control group. We will use an accurate and reliable image analysis technique developed at our department at the University of Nottingham to measure the spinal cord CSA (NeuRoi).[70]

Our primary objective is to assess the CSA at the upper cervical cord (C2−C3) and its rate of atrophy over one year in patients with DPN.

Our secondary objectives are:

1) to evaluate the relationship between upper cervical cord CSA and clinical and other paraclinical measures of diabetes (e.g., routine blood tests for diabetes),

2) to evaluate the relationship between upper cervical cord CSA and clinical and other paraclinical measures of DPN (e.g., NCS),

3) to assess the CSA at the upper cervical cord (C2−C3) and its rate of atrophy over one year in the control groups,

4) (where relevant) to evaluate the relationship of upper cervical cord atrophy in all groups to atrophy in other spinal cord regions (lower cervical cord [C4−C5] and upper midthoracic cord [T4−T5]), brain atrophy, quality of life, anxiety and depression, and inflammatory, metabolic, and genetic markers.

5) to compare spinal cord CSA measurements made by NeuRoi to that of other available software such as SCT.

3. MATERIALS AND METHODS

3-1. Study Design

This is an observational study for MRI-based evaluation of spinal cord atrophy in patients with DPN. The study has a cross-sectional and prospective longitudinal component. The cervical and upper thoracic cord will be quantified on MRI scans using different image analysis software (as described in the following sections and introduction). The measurements made on the spinal cord of participants with DPN

will be compared against that of control groups (as described in the following sections) in the cross-sectional arm of the study. Also, all participants will be followed up after 12 to 18 months to, prospectively, assess and compare their rates of spinal cord atrophy over one year in the longitudinal arm of the study.

In addition to evaluating the spinal cord at different levels, spinal cord atrophy will be compared to brain atrophy in all participants. The relationship between measurements of the spinal cord and other outcome measures of diabetes and DPN (e.g., neurological examination, laboratory tests, or NCS) will be also assessed in participants with diabetes or DPN. In all participants, the relationship between spinal cord atrophy and quality of life, anxiety and depression, and other inflammatory, metabolic, and genetic markers will be investigated.

3-2. Participants

Eligible age and gender matched participants will be recruited to one of the five study groups: 1) diabetic patients with clinical or subclinical DPN (DM+DPN), 2) diabetic patients without DPN (DM-DPN), 3) patients without diabetes and with other polyneuropathies than do not involve the spinal cord (OPN), 4) patients with relapsing-remitting or progressive MS but without diabetes or polyneuropathies (MS), 5) healthy controls without diabetes or polyneuropathies (HC).

Based on previous studies,[55 59] an estimated sample size of 40 for the DM+DPN group (ideally 20 with subclinical DPN and 20 with clinical DPN), 20 for the DM-DPN group, 20 for the OPN group, 15 for the MS group, and 20 for the HC group will be required. All patients with diabetes but without clinical signs and symptoms of DPN

will undergo NCS to look for subclinical DPN. They will then be recruited to the DM+DPN or DM-DPN group accordingly.

Participants must meet all the following inclusion criteria for recruitment: 1) age 18-75 years, 2) ability to give informed consent, 3) ability to speak and understand English language, 4) have a diagnosis consistent with one of the five study groups, with initial symptoms having preceded enrolment in the study by at least 12 months and the condition has been stable for at least 2 months.

Participants will be excluded from the study if they meet any of the following exclusion criteria: 1) extensive cardiovascular and/or cerebrovascular comorbidities, 2) other comorbidities, in particular neurological diseases, that in view of the researcher may interfere with the study, 3) significant spinal or spinal cord disease (other than MS in the MS group), 4) contraindications for MRI, 5) pregnancy or planning for pregnancy.

3-3. Magnetic Resonance Imaging

All participants will undergo an MRI on a 3T Philips Ingenia wide bore system scanner at Sir Peter Mansfield Imaging Centre (SPMIC) of the University of Nottingham once at recruitment and once after 12 to 18 months. The MRI protocol includes T1-weighted (3D MPRAGE) and FLAIR (fluid-attenuated inversion recovery) sequences of the brain and the cervical and upper thoracic cord (down to T4-T5) in addition to bFFE (balanced fast field echo) sequences of C2-C3, C4-C5, and T4-T5 cord segments for a higher resolution axial image of the spinal cord. The overall scan duration will be about 40 to 60 minutes.

Quantification of the spinal cord will be performed using both the NeuRoI and SCT image analysis software. Brain volumes will be obtained using the FMRIB (Oxford Centre for Functional MRI of the Brain) Software Library (FSL) for analysis of T1-weighted brain MRI images.

3-4. Other Investigations

Demographic and clinical data of all participants will be recorded on the Case Report Form (CRF) at recruitment and follow-up. Clinical data will include details of participants' history, physical examination, and weight and height measurements for BMI and BSA. The neurological examination will include a detailed assessment of polyneuropathy in all participants which will also be used to rule out the presence of polyneuropathy in the DM-DPN, MS, and HC groups. All participants will undergo vibration perception threshold testing using a Harwood Neurothesiometer. In addition, participants with diabetes but without clinical signs and symptoms of DPN will undergo NCS to look for possible subclinical DPN.

Participants of the DM+DPN and OPN groups would have had NCS as part of their routine clinical care. The date and measurements of NCS will be recorded in the CRF.

All participants will complete the Michigan Neuropathy Screening Instrument (MNSI), two quality of life questionnaires (EQ-5D-5L and SF-36), the Hospital Anxiety and Depression Scale (HADS), the Visual Analogue Scale (VAS) for pain, and the Neuropathic Pain 4 Questions (DN4) for the probability of neuropathic pain. Participants with diabetes will also complete the Diabetes Quality of Life (D-QoL), and Problem Areas in Diabetes (PAID) questionnaires. Participants with polyneuropathy will also complete the Leeds Assessment of Neuropathic Symptoms

and Signs (LANSS) and Neuropathic Pain Scale (NPS) questionnaires. Participants with MS will also complete the MS quality of life questionnaires including MusiQoL and MSQoL-54 and the MS Impact Scale version 29 (MSIS-29).

Blood samples for measuring glucose profile, lipid profile, and renal function will be collected if the results are not available within the previous 2 months. Also, blood samples will be collected for assessing inflammatory, metabolic, and genetic markers. These markers include IL-33, TNF, Osteopontin, MMP, and genetic polymorphisms associated with MS, DM, and brain and spinal cord atrophy. Urine samples will be obtained for protein and validation of some of the above biomarkers. The samples will be saved in the licenced freezer in the laboratory of Prof. Constantinescu under the Human Tissue Act 2004.

All the above investigations will be performed at recruitment and after 12 to 18 months.

3-5. Statistical Analysis

The spinal cord measurements between the study groups will be compared using the independent-samples t-test or Mann Whitney U test (depending on the normality of distribution). The spinal cord measurements of the study groups in the longitudinal arm of the study will be compared by paired-samples t-test and one-way repeated measures ANOVA. Regression analysis will be used to identify factors associated with spinal cord atrophy.

4. RESULTS

As of 17 March 2020, when SPMIC closed down due to the Coronavirus disease 2019 outbreak, we had recruited a total of 6 participants of whom 3 were in the HC group, 1 in the DM+DPN group, 1 in the OPN group, and 1 in the MS group. We will continue recruitment as soon as SPMIC restarts scanning healthy volunteers or patients.

5. DISCUSSION

The optimal strategy for the early diagnosis of DPN is unknown. Routine clinical examination and NCS detect polyneuropathy only when it has caused irreversible nerve damage. Therefore, treatments to modify the course of DPN have not been developed. Also, these tools do not provide an accurate and reliable measure of DPN progression to assess the efficacy of potential treatments.

For decades, it has been known that the spinal cord is involved in DPN. However, it was only after the detection of spinal cord atrophy in patients with subclinical and clinical DPN using MRI-based quantification techniques that spinal cord atrophy was introduced as a potential marker for early detection of DPN. A cross-sectional study showed that spinal cord atrophy is only present in patients with DPN compared to diabetic patients without DPN and that it precedes clinical manifestations of DPN. To our knowledge, these findings have not been confirmed in any longitudinal studies. Therefore, in this study, in addition to re-evaluating the above observations, we intend to assess the rate of spinal cord atrophy over time in diabetic patients and investigate its use as an additional modality for monitoring DPN.

Chapter 2

Coronavirus Disease 2019

and

Multiple Sclerosis

This chapter has been removed to avoid duplication of thesis.

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Appendix 2-A

Letters

Self-diagnosed COVID-19 in people with multiple sclerosis: a community-based cohort of the UK MS Register

INTRODUCTION

In the early phases of the UK COVID-19 outbreak, in the absence of clear evidence about the risks for people with multiple sclerosis (pwMS) and those taking immunomodulatory disease-modifying therapies (DMT), we launched a community-based study as part of the UK MS Register (UKMSR). We intended to capture the picture of COVID-19 among pwMS and their risk of contracting the disease. Here, we report our findings from 17 March to 24 April 2020.

METHODS

The COVID-19 study (clinicaltrials.gov: NCT04354519) is a prospective observational cohort launched on 17 March 2020 as part of the UKMSR (Ethics:16/SW/0194). PwMS completed a specific COVID-19 related survey which was combined with data held from before the pandemic where available. The primary outcome of the study is participant-reported self-diagnosis of COVID-19. Participants were asked if their diagnosis was confirmed by testing—the available test in the UK was reverse transcriptase-PCR. Participants reported if their sibling without MS, closest in age who was not living with them, had self-diagnosed COVID-19. The likelihood of having COVID-19 was assessed using multivariable regression analysis with the variables: age, gender, ethnicity, MS duration and type, self-isolation and DMTs. DMTs were considered after stratifying based on moderate-efficacy versus high-efficacy therapies (table 1). Disability was assessed using the last recorded web-based Expanded Disability Status Scale (webEDSS) or MS Impact Scale v2 (MSIS-29v2).

RESULTS

As of 24 April, out of 3910 participants, 237 (6.1% (95% CI 5.3% to 6.8%)) reported self-diagnosed COVID-19 among whom 54 (22.8% (17.5% to 28.2%)) also had a diagnosis by a healthcare professional based on symptoms and 37 (15.6% (11.2% to 20.6%)) a confirmed diagnosis by testing. Three participants reported hospitalisation due to COVID-19. No deaths were reported.

Among 1283 siblings without MS, 79 (6.2%) had a reported diagnosis of COVID-19. Adjusting for age and gender, the likelihood of contracting COVID-19 in pwMS was similar to siblings (OR 1.180 (0.888 to 1.569)).

Seven hundred and fifty-nine of 3812 participants reported that they were self-isolating and that they had been self-isolating for at least 2 weeks before symptom onset if they had COVID-19. Of these, 2 (0.3% (0% to 0.7%)) had self-diagnosed COVID-19 whereas 137 of 3053 participants not self-isolating (4.5% (3.8% to 5.2%)) had the disease ($p<0.001$). Among participants with confirmed COVID-19, 94.6% (86.5% to 100%) were not self-isolating which was higher than those without the disease (79.9% (78.7% to 81.3%), $p=0.023$). Self-isolating participants were slightly older than those not self-isolating ($p<0.001$). A lower proportion of participants on DMTs were self-isolating compared with those not taking DMTs (18.1% (16.4% to 20%) vs 21.5% (19.6% to 23.3%), $p=0.01$). Rate of self-isolation in participants taking high-efficacy DMTs was similar to those not taking DMTs and higher than those taking moderate-efficacy DMTs (21.3% vs 21.4% and 16.5%, $p=0.993$ and $p=0.014$, respectively). More participants with progressive MS (PMS) were self-isolating compared with relapsing-remitting MS (RRMS) (23.2% (21% to 25.3%) vs 17.9% (16.3% to 19.5%), $p<0.001$).

Using self-diagnosed and confirmed COVID-19 as outcomes, 3714 and 3618 participants were included in the regression analysis, respectively. Self-isolation predicted a lower likelihood of having self-diagnosed COVID-19 (OR 0.064 (0.016 to 0.259)) but not confirmed COVID-19.

Participants on DMTs were less likely to have self-diagnosed COVID-19 (OR 0.640 (CI 0.428 to 0.957)), which remained significant after removing

Table 1 Distribution of individual disease-modifying therapies (DMTs) among participants of the COVID-19 study

DMT	Total (n=3907), n (%)	Self-diagnosed COVID-19 (n=236), n (%)	Confirmed COVID-19 (n=37), n (%)
None	2088 (53.4)	116 (49.2)	11 (29.7)
Beta-interferons*	232 (5.9)	11 (4.7)	1 (2.7)
Glatiramer acetate*	196 (5)	18 (7.6)	3 (8.1)
Dimethyl fumarate*	446 (11.4)	32 (13.6)	7 (18.9)
Teriflunomide*	93 (2.4)	2 (0.8)	0 (0)
Fingolimod*	235 (6)	15 (6.4)	4 (10.8)
Siponimod	3 (0.1)	0 (0)	0 (0)
Ocrelizumab†	193 (4.9)	14 (5.9)	4 (10.8)
Natalizumab†	231 (5.9)	19 (8.1)	5 (13.5)
Cladribine†	73 (1.9)	2 (0.8)	0 (0)
Alemtuzumab†	93 (2.4)	5 (2.1)	2 (5.4)
HSCT†	2 (0.1)	0 (0)	0 (0)
Mitoxantrone†	0 (0)	0 (0)	0 (0)
Others‡	16 (0.4)	2 (0.8)	0 (0)
Unknown	6 (0.2)	0 (0)	0 (0)

*Defined as moderate-efficacy DMTs.
†Defined as high-efficacy DMTs.
‡Including rituximab, ofatumumab, ublituximab, vedolizumab, ponesimod, azathioprine, mycophenolate mofetil and methotrexate.
HSCT, hematopoietic stem cell transplantation.

self-isolating participants (OR 0.633 (0.402 to 0.998)). High-efficacy DMTs reduced the likelihood of self-diagnosed COVID-19 compared with no DMTs (OR 0.540 (0.311 to 0.938)) but not compared with moderate-efficacy DMTs. There was no significant association between taking DMTs and having confirmed COVID-19. It was not possible to do a formal statistical test for the association between individual DMTs and COVID-19 due to small numbers (table 1).

Younger age was associated with increased likelihood of having self-diagnosed (OR 1.043 (1.022 to 1.064)) and confirmed (OR 1.048 (1.009 to 1.087)) COVID-19.

Participants with PMS were less likely to have self-diagnosed (OR 0.429 (0.241 to 0.763)) or confirmed (OR 0.119 (0.015 to 0.967)) COVID-19 compared with those with RRMS, but this effect disappeared after excluding participants who were self-isolating.

Including webEDSS (n=2808) and physical MSIS-29v2 (n=3192) as additional predictors in the analysis showed no significant association with the likelihood of contracting COVID-19.

The gender distribution was similar between participants with and without COVID-19. More participants with self-diagnosed COVID-19 reported themselves as having any ethnicity other than white compared with those without the disease (6.9% (3.9% to 10.1%) vs 3.8% (3.2% to 4.4%), p=0.019). Gender and ethnicity did not affect the likelihood of having COVID-19.

DISCUSSION

We report initial findings of an ongoing community-based COVID-19 study in a large UK-wide population of pwMS which coincided with the peak of the COVID-19 outbreak in the UK.[1] We show that pwMS taking immunomodulatory treatments do not have an increased risk of contracting COVID-19. We did not find individual DMTs to be noticeably over-represented among pwMS with COVID-19.

The incidence of COVID-19 in our population of pwMS was not higher than that of the general population,[2] and pwMS were not at a higher risk of having COVID-19 compared with their siblings without MS. The low hospitalisation rate in our population is possibly due to its patient-reported nature where hospitalised pwMS would fail to respond to the surveys.

The observation that self-isolating pwMS had a lower risk of COVID-19 was not unexpected. We found older pwMS and those with PMS were less likely to have COVID-19. This could be because they were self-isolating more. Similar to previous reports, we found evidence that pwMS with any ethnicity other than white had a higher chance of contracting COVID-19,[3] but larger numbers are required to confirm this.

When this study launched, there was no accurate or accessible test to diagnose COVID-19. Therefore, we decided to set a diagnosis of COVID-19 made by participants, based on their symptoms, as the primary outcome of the study. This approach has also been adopted in other large-scale studies and is in line with the UK government policy not to seek medical advice for mild symptoms of COVID-19.[4 5]

In conclusion, during a period with strict precautions in place to prevent the spread of COVID-19, pwMS and those taking DMTs are not at an increased risk of contracting the disease.

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Appendix 2-B

Directed Acyclic Graph (DAG)

Chapter 2. Self-reported COVID-19 in people with MS

The DAG in Figure 2-B.1 was used to determine the minimal set of adjustments that needed to be included in the multivariable binomial logistic regression analysis to estimate the association between demographic and clinical characteristics of people with MS and contracting COVID-19.

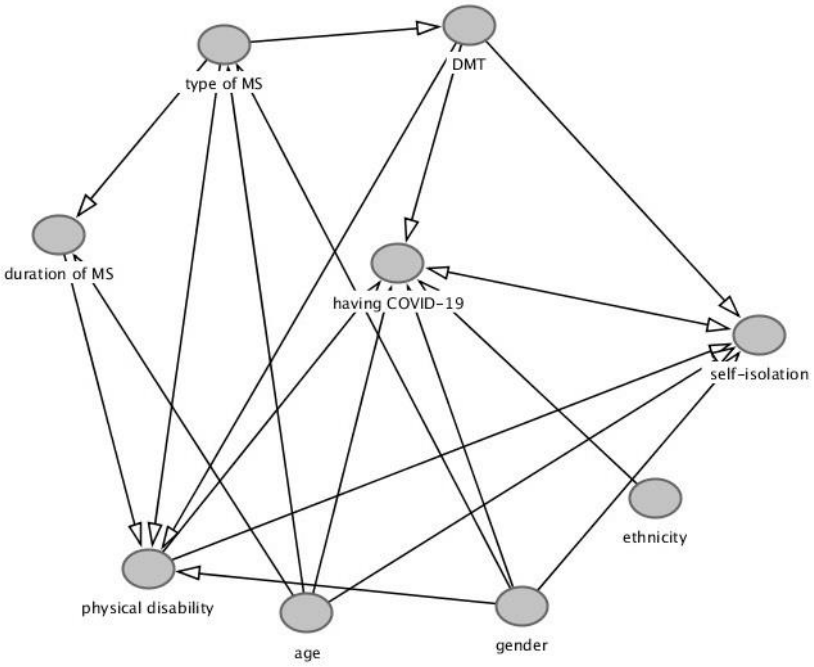


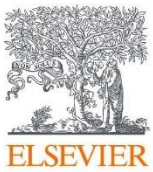
Figure 2-B.1. The directed acyclic graph used for identifying confounders in Chapter 2 of the thesis.

The following code can be used at http://www.dagitty.net/dags.html to replicate the DAG:

```
dag {
bb="0,0,1,1"
"duration of MS" [pos="0.298,0.458"]
"having COVID-19" [pos="0.485,0.483"]
"physical disability" [pos="0.347,0.739"]
"self-isolation" [pos="0.684,0.543"]
"type of MS" [pos="0.389,0.298"]
DMT [pos="0.524,0.282"]
```

```
age [pos="0.435,0.777"]
ethnicity [pos="0.626,0.680"]
gender [pos="0.553,0.771"]
"duration of MS" -> "physical disability"
"having COVID-19" <-> "self-isolation"
"physical disability" -> "having COVID-19"
"physical disability" -> "self-isolation"
"type of MS" -> "duration of MS"
"type of MS" -> "physical disability"
"type of MS" -> DMT
DMT -> "having COVID-19"
DMT -> "physical disability"
DMT -> "self-isolation"
age -> "duration of MS"
age -> "having COVID-19"
age -> "self-isolation"
age -> "type of MS"
ethnicity -> "having COVID-19"
gender -> "having COVID-19"
gender -> "physical disability"
gender -> "self-isolation"
gender -> "type of MS"
}
```

Appendix 3-A



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Original article

COVID-19 is associated with new symptoms of multiple sclerosis that are prevented by disease modifying therapies

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ABSTRACT

Background: Infections can trigger exacerbations of multiple sclerosis (MS). The effects of the coronavirus disease 2019 (COVID-19) on MS are not known. The aim of this study was to understand the impact of COVID-19 on new and pre-existing symptoms of MS.
Methods: The COVID-19 and MS study is an ongoing community-based, prospective cohort study conducted as part of the United Kingdom MS Register. People with MS and COVID-19 were invited by email to complete a questionnaire about their MS symptoms during the infection. An MS exacerbation was defined as developing new MS symptoms and/or worsening of pre-existing MS symptoms.
Results: Fifty-seven percent (230/404) of participants had an MS exacerbation during their infection; 82 developed new MS symptoms, 207 experienced worsened pre-existing MS symptoms, and 59 reported both. Disease modifying therapies (DMTs) reduced the likelihood of developing new MS symptoms during the infection (OR 0.556, 95%CI 0.316–0.978). Participants with a higher pre-COVID-19 webEDSS (web-based Expanded Disability Status Scale) score (OR 1.251, 95%CI 1.060 1.478) and longer MS duration (OR 1.042, 95%CI 1.009 1.076) were more likely to experience worsening of their pre-existing MS symptoms during the infection.
Conclusion: COVID-19 infection was associated with exacerbation of MS. DMTs reduced the chance of developing new MS symptoms during the infection.

1. Introduction

The role of systemic infections in provoking exacerbations of multiple sclerosis (MS) is well described (Marrodan et al., 2019). The coronavirus disease 2019 (COVID-19) is a viral infection, the effects of which on MS exacerbations have not been established. Understanding the impact of COVID-19 on MS symptoms will allow for thorough counselling of people with MS regarding the risk of infection during periods of community transmission.

Potential safety concerns about using immunosuppressive MS disease modifying therapies (DMTs) during the COVID-19 pandemic (Sharifian-Dorche et al., 2021), along with disruptions to MS services

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(Moss et al., 2020), have resulted in changes to the treatment plans of many people with MS. However, a decrease in the use of DMTs during the pandemic could lead to excessive MS relapses. Further understanding of the relationship between COVID-19, MS relapses and DMTs will inform decision-making about altering or delaying treatment with DMTs.

In this paper, we study the impact of COVID-19 on pre-existing and new symptoms of MS in a large cohort of people with MS and COVID-19. We also assess potential factors associated with COVID-19 related MS exacerbations.

2. Materials and methods

The COVID-19 and MS study is an ongoing national community-based, prospective cohort study conducted as part of the United Kingdom (UK) MS Register (UKMSR) (Evangelou et al., 2021). People with MS report whether they have had symptoms consistent with COVID-19, whether the diagnosis was confirmed by a healthcare provider based on their clinical or laboratory findings, and whether they have been admitted to a hospital because of their infection (Evangelou et al., 2021).

People with MS and symptoms consistent with COVID-19 were invited to complete a questionnaire about their MS symptoms during or soon after the infection between 20th of July 2020 and 25th of January 2021. We asked participants about any new or worsened pre-existing MS symptoms (Appendix A). Here, we report our cross-sectional findings according to the STROBE guidelines (STROBE Statement, 2007).

We defined an MS exacerbation as developing new MS symptoms, worsening of pre-existing MS symptoms, or experiencing both during a COVID-19 infection. We asked participants about limitation in daily activities caused by the new symptoms and classified them as mild (no limitation), moderate (less than 50% limitation), or severe (more than 50% limitation).

We correlated the COVID-19 and MS symptoms data with information held by the UKMSR on participants' demographics (age, sex, and ethnicity), clinical characteristics (MS type, disease duration from diagnosis, and DMTs), most recent recorded web-based Expanded Disability Status Scale (webEDSS) scores (scored 0 – 10, with higher scores indicating more neurological impairment) from before their infection (Leddy et al., 2013), and most recent Hospital Anxiety and Depression Scale scores (scored 0 – 21, with scores ≥11 considered as probable cases of anxiety or depression) (Marrie et al., 2018).

2.1. Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA; 2019).

Continuous data were compared using the independent samples *t*-test, if normally distributed (mean [standard deviation, SD]) or the Mann-Whitney U test, when not normally distributed (also used for comparing ordinal variables; median [interquartile range, IQR]). Categorical variables were analysed using the Chi-square test (or Fischer's exact test if expected count ≤5). For variables with missing data, the number of valid values is stated.

The association between different dependent (developing new MS symptoms, worsening of pre-existing MS symptoms) and independent variables (age, sex, type of MS, MS disease duration, pre-COVID-19 webEDSS score, DMT use) was assessed using univariable or multivariable binomial logistic regression analysis. To avoid introducing bias by controlling for colliders and mediators in the regression analyses models, directed acyclic graphs (DAGs) were built to determine confounding factors for individual regression analyses (Fig. B.1 and Appendix B) (Greenland et al., 1999; Rohrer, 2018). Confounding factors controlled for in each analysis have been stated. Listwise deletion was implemented for missing data. The results of the regression analyses are presented as odds ratio (OR) and 95% confidence intervals (95% CI).

2.2. Standard protocol approvals, registrations, and patient consents

Ethical approval for UKMSR studies was obtained from South West-Central Bristol Research Ethics Committee (16/SW/0194). Participants provided informed consent online. The study is registered on clinicaltrials.gov: NCT04354519.

2.3. Data availability policy

Data are stored on the UKMSR Secure e-Research Platform at Swansea University Medical School. Line level data cannot be released, but qualified researchers, subject to governance, can request access to data.

3. Results

We invited 978 people with MS and COVID-19 to complete the MS symptoms questionnaire and 404 (41%) responded within a median (IQR) duration of 14 (9 – 17) weeks from reporting a diagnosis of COVID-19 (Table 1).

Two hundred and thirty (57%) participants had an MS exacerbation, with 82 (20%) developing new symptoms, 207 (51%) experiencing worsened pre-existing symptoms, and 59 (15%) reporting both during their COVID-19 infection.

Ninety-seven percent ($n = 222$) of participants with an MS exacerbation (80 with new MS symptoms and 199 with worsened pre-exiting MS symptoms) had fever during their infection compared to 68%

Table 1
Demographic and clinical characteristics of participants and non-participants.

	Participants ($n = 404$)	Non-participants ($n = 574$)	*p* value	
Age, years, mean (SD)	50 (11)	48 (11)	0.001	
Female, n (%)	307 (76)	456 (79.4)	0.434	
White ethnicity, n (%)	380 (94.1)	538 (93.7)	0.832	
Pre-COVID-19 webEDSS score [a], median (IQR)	4.5 (3 – 6.5) $n = 248$	4 (3 – 6.5) $n = 288$	0.776	
MS type, n (%)				
	RRMS	277 (68.6)	415 (72.3)	0.018
	SPMS	65 (16.1)	99 (17.2)	
	PPMS	39 (9.7)	26 (4.5)	
	Unknown	23 (5.7)	34 (5.9)	
MS disease duration, years, median (IQR)	11 (5 – 18) $n = 395$	10 (5 – 17) $n = 547$	0.106	
DMTs, n (%)	193 (47.8)	301 (52.4)	0.151	
Beta interferons	21 (5.2)	39 (6.8)		
Glatiramer acetate	22 (5.4)	37 (6.5)		
Teriflunomide	7 (1.7)	14 (2.4)		
Dimethyl fumarate	58 (14.4)	72 (12.6)		
Fingolimod	24 (5.9)	35 (6.1)		
Siponimod	0 (0)	1 (0.2)		
Natalizumab	24 (5.9)	44 (7.7)		
Ocrelizumab	14 (3.5)	33 (5.8)		
Cladribine	7 (1.7)	9 (1.6)		
Alemtuzumab	13 (3.2)	15 (2.6)		
Others [b]	3 (0.7)	1 (0.2)		
Confirmed COVID-19, n (%)	108 (26.7)	168 (29.3)	0.386	
Hospitalized due to COVID-19, n (%)	8 (2)	9 (1.6)	0.620	

DMTs Disease Modifying Therapies; IQR Interquartile Range; PPMS Primary Progressive MS; RRMS Relapsing Remitting MS; SD Standard Deviation; SPMS Secondary Progressive MS; webEDSS web-based Expanded Disability Status Scale.

[a] The median (IQR) duration from recording the webEDSS score to reporting COVID-19 was 7 (3 – 16.75) weeks for participants and 11 (6 – 23.75) weeks for non-participants ($p < 0.001$).

[b] Participants were taking Ponesimod (n 1) and Rituximab (n 2) and the non-participant was taking Azathioprine.

($n = 72$) of participants without an MS exacerbation ($p < 0.001$). Six (3%) participants with an MS exacerbation (2 with new MS symptoms and all 6 with worsened pre-existing MS symptoms) and 2 (1%) participants without an MS exacerbation were hospitalized due to COVID-19 ($p = 0.296$).

The rate of MS exacerbations was not significantly different between participants with ($n = 108$) and without ($n = 296$) a confirmed diagnosis of COVID-19 (63.9% vs 54.4%, $p = 0.088$).

A higher proportion of participants with anxiety and/or depression reported an MS exacerbation during their infection compared to participants without anxiety or depression (68% [78/114] vs 51% [109/212], $p = 0.003$), with 32% ($n = 36$) and 14% ($n = 30$) reporting new MS symptoms, respectively, and 61% ($n = 69$) and 48% ($n = 101$) reporting worsened pre-existing MS symptoms, respectively.

Thirty-nine percent (77/196) of the participants with an MS exacerbation required additional support for their daily activities during COVID-19 infection, as opposed to only 6% (7/114) of the participants without an exacerbation ($p < 0.001$).

3.1. New MS symptoms

Among the 82 participants with new MS symptoms during the infection, the most reported new symptoms were sensory, motor, or both ($n = 58$; 71%) (Table 2). Some COVID-19 symptoms such as fatigue, memory problems, or mobility problems can mimic MS symptoms. Most participant who reported fatigue ($n = 18$), memory problems ($n = 17$), or mobility problems ($n = 24$) as part of their new MS symptoms during the infection had additional non-COVID-19 related neurological symptoms including sensory, motor, visual, or balance problems (89%, 88%, and 71%, respectively).

Table 2
Reported new multiple sclerosis symptoms during COVID-19 infection.

	N (%)	
Symptoms [a]	82 (100)	
Weakness	27 (6.7)	
	Mild	6 (22.2)
	Moderate	14 (51.9)
	Severe	7 (25.9)
Sensory symptoms (numbness, pins and needles, or pain)	43 (10.6)	
	Mild	12 (30.8)
	Moderate	24 (61.5)
	Severe	7 (17.9)
Balance problems	24 (5.9)	
	Mild	5 (20.8)
	Moderate	14 (58.3)
	Severe	5 (20.8)
Bladder or bowel problems	15 (3.7)	
	Mild	4 (28.6)
	Moderate	6 (42.9)
	Severe	5 (35.7)
Visual problems (blurred vision or double vision)	12 (3)	
	Mild	5 (41.7)
	Moderate	3 (25)
	Severe	4 (33.3)
Fatigue	18 (4.5)	
	Mild	3 (16.7)
	Moderate	6 (33.3)
	Severe	9 (50)
Memory problems	17 (4.2)	
	Mild	3 (17.6)
	Moderate	9 (52.9)
	Severe	5 (29.4)
Mobility problems	24 (5.9)	
	Mild	3 (12.5)
	Moderate	13 (54.2)
	Severe	8 (33.3)
Others [b]	10 (2.5)	

[a] Symptoms causing no limitation in daily activities were considered as mild, symptoms causing less than 50% limitation in daily activities as moderate, and symptoms causing more than 50% limitation in daily activities as severe.
[b] Other new MS symptoms included spasms, speech or swallowing difficulties, tremor, or vertigo.

Sixteen (20%) participants with new MS symptoms during their infection had mild, 40 (49%) had moderate, and 26 (32%) had severe symptoms. None were treated with steroids.

Taking DMTs reduced the likelihood of developing new MS symptoms during the infection (adjusted OR 0.556, 95% CI 0.316 – 0.978 for type of MS) (Table 3). The results were similar after adjusting for age, sex, pre-COVID-19 webEDSS score and type of MS (adjusted OR 0.430, 95% CI 0.198 – 0.931). We did not formally test the association between individual DMTs and developing new MS symptoms due to the small number of participants on individual DMTs; however, it seemed that a higher proportion of participants without new MS symptoms during their infection were taking fingolimod, ocrelizumab, or cladribine compared to participants who developed new symptoms (Table 4).

Thirty-six (44%) participants with new MS symptoms reported recovery from these symptoms; 21 (26%) recovered within three weeks. Among the 46 participants who had not reported recovery, the median (IQR) duration from reporting COVID-19 to reporting persistence of the symptoms was 14 (10 – 17) weeks.

3.2. Pre-existing MS symptoms

Among the 207 participants with worsened pre-existing MS symptoms during the infection (Table 5), 190 (92%) reported this worsening to be the same as ($n = 91$) or worse than ($n = 99$) their previous non-COVID-19 systemic infection.

The pre-existing MS symptoms of participants with a higher pre-COVID-19 webEDSS score (adjusted OR 1.251, 95% CI 1.060 – 1.478) and longer MS disease duration (adjusted OR 1.042, 95% CI 1.009 – 1.076) were more likely to worsen during the infection (Table 3).

Sixty-three (30%) participants who experienced worsening of their pre-existing MS symptoms during the infection reported returning to baseline; 42 (20%) recovered within three weeks. Among the 144 participants who had not returned to baseline, the median (IQR) duration from reporting COVID-19 to responding to the questionnaire was 14 (9 – 16) weeks.

4. Discussion

This large community-based study found that 57% of people with MS and COVID-19 experience an MS exacerbation during their infection, including 20% who develop new MS symptoms. Previous studies have demonstrated an increased risk of MS exacerbations associated with other infections (Marrodan et al., 2019), but the rates (9–41%) (Buljevac et al., 2002; Correale et al., 2006; Edwards et al., 1998; Panitch, 1994; Sibley et al., 1985) are lower than COVID-19 related exacerbations reported in this study. This difference could suggest a difference between COVID-19 and other common systemic infections in inducing MS exacerbations; however, it should be noted that our findings could have been influenced by recall bias. We could not objectively assess the reported new MS symptoms by neurological examination to confirm that they were relapses due to the restrictions caused by the pandemic. Previously, it has been shown that relapses reported by people with MS are often also diagnosed as relapses by clinicians (Schriefer et al., 2020). Our study did not include a control group of people with MS without COVID-19 and therefore, we could not assess the absolute risk of MS exacerbations associated with COVID-19.

An association between DMT use and reduction of infection-related exacerbations of MS has not been conclusively established (Buljevac et al., 2002; Panitch, 1994). We found that taking a DMT reduces the probability of developing new MS symptoms during COVID-19 infection by 44%, which is consistent with the overall relapse rate reduction, in the absence of infection, observed in clinical trials of current DMTs (De Angelis et al., 2018). Our data suggest that different DMTs might have a

Table 3
Factors associated with changes in symptoms of multiple sclerosis.

	Multivariable regression analysis				Univariable regression analysis		
	OR	95% CI	N [a]	Adjustments	OR	95% CI	N [a]
Developing new MS symptoms ($n = 82$) compared to no new MS symptoms ($n = 322$)							
Age (one-year increase)	No adjustment was required.				0.997	0.975–1.019	404
Male (vs female)	No adjustment was required.				0.550	0.289–1.048	403
PMS (vs RRMS)	1.532	0.814–2.883	395	Age, Sex, MS disease duration	1.337	0.779–2.296	404
MS disease duration (one-year increase)	1.024	0.991–1.059	395	Age	1.017	0.989–1.046	395
Pre-COVID-19 webEDSS score (one-point increase)	1.108	0.929–1.322	248	Age, Sex, Type of MS, Taking DMTs	1.059	0.914–1.226	248
Taking DMTs	**0.556**	**0.316–0.978**	404	Type of MS	0.563	0.341–0.928	404
Worsening of pre-existing MS symptoms ($n = 207$) compared to no worsening ($n = 128$) [b]							
Age (one-year increase)	No adjustment was required.				1.016	0.995–1.037	335
Male (vs female)	No adjustment was required.				0.640	0.381–1.077	335
PMS (vs RRMS)	1.147	0.625–2.106	327	Age, Sex, MS disease duration	1.328	0.786–2.243	335
MS disease duration (one-year increase)	**1.042**	**1.009–1.076**	327	Age	1.044	1.015–1.074	327
Pre-COVID-19 webEDSS score (one-point increase)	**1.251**	**1.060–1.478**	208	Age, Sex, Type of MS, Taking DMT	1.163	1.017–1.330	208
Taking DMTs	1.186	0.716–1.966	335	Type of MS	1.047	0.673–1.627	335

CI Confidence Interval; DMTs Disease Modifying Therapies; MS Multiple Sclerosis; OR Odds Ratio; PMS Progressive MS, which includes primary and secondary progressive MS; webEDSS web-based Expanded Disability Status Scale.
[a] Number of participants included in the analysis after listwise deletion of missing data.
[b] Sixty-nine participants did not recall whether their pre-existing MS symptoms had become worse or not during their COVID-19 infection.

Table 4
Characteristics of participants with and without new symptoms of multiple sclerosis during COVID-19 infection.

	With new MS symptoms $n = 82$	Without new MS symptoms $n = 322$	p value	
Age, years, mean (SD)	50 (11)	50 (11)	0.784	
Female, n (%)	68 (82.9)	239 (74.2)	0.066	
White ethnicity, n (%)	79 (96.3)	301 (93.5)	0.327	
Pre-COVID-19 webEDSS score, median (IQR)	5 (2.875 – 6.5) $n = 50$	4 (3 – 6.5) $n = 198$	0.481	
MS type, n (%)				
RRMS	53 (64.6)	224 (69.6)	0.589	[a]
SPMS	14 (17.1)	51 (15.8)		
PPMS	11 (13.4)	28 (8.7)		
Unknown	4 (4.9)	19 (5.9)		
MS disease duration, years, median (IQR)	11.5 (5 – 20.5) $n = 80$	11 (6 – 17) $n = 315$	0.564	
DMTs [b], n (%)	30 (36.6)	163 (50.6)	0.023	
Beta interferons	4 (13.3)	17 (10.4)		
Glatiramer acetate	6 (20)	16 (9.8)		
Teriflunomide	2 (6.7)	5 (3.1)		
Dimethyl fumarate	8 (26.7)	50 (30.7)		
Fingolimod	2 (6.7)	22 (13.5)		
Natalizumab	5 (16.7)	19 (11.7)		
Ocrelizumab	1 (3.3)	13 (8)		
Cladribine	0 (0)	7 (4.3)		
Alemtuzumab	2 (6.7)	11 (6.7)		
Others [c]	0 (0)	3 (1.8)		
Required more help [d], n (%)	28 (39.4)	68 (23.9)	0.009	

DMTs Disease Modifying Therapies; IQR Interquartile Range; PPMS Primary Progressive MS; RRMS Relapsing Remitting MS; SPMS Secondary Progressive MS; webEDSS web-based Expanded Disability Status Scale.
[a] One cell (12.5%) has expected count less than 5.
[b] Percentages of individual DMTs are calculated based on the total number of participants taking DMTs in each group.
[c] Participants were taking Ponesimod (n 1) and Rituximab (n 2).
[d] During their COVID-19 infection than before.

variable effect in preventing COVID-19 related new MS symptoms. This very preliminary finding is interesting but needs to be confirmed in larger case-control studies to (1) provide a precise estimation of the association between DMT use and infection related relapses, and (2) compare this association to the effectiveness of DMTs in preventing non-infection related relapses.

Studies have suggested that infection-related exacerbations can be more severe and prolonged compared to exacerbations not induced by an infection (Buljevac et al., 2002; Correale et al., 2006). In our study, the MS exacerbation of many participants had not resolved three months after their COVID-19 infection. Most individuals with COVID-19 related worsening of their MS symptoms reported a deterioration that was worse than or similar to their previous non-COVID-19 infection. This finding could have been influenced by recall bias, however. In addition, most individuals reported that their new MS symptoms resulted in limitation of their daily activities.

We wondered whether people had regarded their COVID-19 symptoms, such as fatigue or cognitive problems that can mimic MS symptoms, as deterioration of their MS. Can we truly distinguish MS deterioration from some systemic symptoms of COVID-19? We cannot answer this question with confidence without paraclinical tests, but we found that most individuals with fatigue, memory, or mobility problems also reported other neurological symptoms suggestive of MS.

Although more individuals with anxiety or depression reported an MS exacerbation during their COVID-19 infection than individuals without anxiety or depression, the rate of MS exacerbations was above 50% in both groups, suggesting that over-reporting of symptoms linked to anxiety or depression has not driven these results (Merckelbach et al., 2019).

5. Conclusions

In this study, we demonstrate that COVID-19 is associated with MS exacerbations. This finding highlights the importance of protecting people with MS against the infection which is now feasible with the increasing number of COVID-19 vaccines. Fewer people taking DMTs experience new neurological symptoms following COVID-19, and, therefore, it is important to consider carefully before altering or delaying treatment with DMTs because of concerns about their safety during the pandemic.

Study funding

The research was supported by the UK MS Society (funding reference 131).

Table 5
Characteristics of participants with and without worsened pre-existing symptoms of multiple sclerosis during COVID-19 infection.

	With worsened pre-existing MS symptoms $n = 207$	Without worsened pre-existing MS symptoms $n = 128$ [a]	*p* value	
Age, years, mean (SD)	51 (11)	49 (11)	0.140	
Female, n (%)	166 (80.2)	93 (72.7)	0.176	
White ethnicity, n (%)	197 (95.2)	117 (91.4)	0.167	
Pre-COVID-19 webEDSS score, median (IQR)	4.5 (3 – 6.5) $n = 133$	4 (2.5 – 6.5) $n = 75$	0.035	
MS type, n (%)				
	RRMS	138 (66.7)	90 (70.3)	0.648
	SPMS	36 (17.4)	18 (14.1)	
	PPMS	21 (10.1)	10 (7.8)	
	Unknown	12 (5.8)	10 (7.8)	
MS disease duration, years, median (IQR)	12 (7 – 19) $n = 203$	8 (4 – 15.75) $n = 124$	0.001	
DMTs [b], n (%)	101 (48.8)	61 (47.7)	0.840	
Beta interferons	9 (8.9)	9 (14.8)		
Glatiramer acetate	11 (10.9)	6 (9.8)		
Teriflunomide	3 (3)	1 (1.6)		
Dimethyl fumarate	36 (35.6)	14 (23)		
Fingolimod	13 (12.9)	9 (14.8)		
Natalizumab	13 (12.9)	8 (13.1)		
Ocrelizumab	6 (5.9)	5 (8.2)		
Cladribine	3 (3)	4 (6.6)		
Alemtuzumab	5 (5)	5 (8.2)		
Others [c]	2 (1.2)	0 (0)		
Required more help [d], n (%)	70 (39.8)	8 (6.6)	<0.001	

DMTs Disease Modifying Therapies; IQR Interquartile Range; PPMS Primary Progressive MS; RRMS Relapsing Remitting MS; SPMS Secondary Progressive MS; webEDSS web-based Expanded Disability Status Scale.

[a] Sixty-nine participants did not recall whether their pre-existing MS symptoms had become worse or not during their COVID-19 infection.

[b] Percentages of individual DMTs are calculated based on the total number of participants taking DMTs in each group.

[c] Participants were taking Ponesimod (n 1) and Rituximab (n 1).

[d] During their COVID-19 infection than before.

Declaration of Competing Interest

AG, RMM and KTD have received funding from the UK MS society. AG has received speaker honoraria from the MS Academy.

RH reports no conflicts of interest.

AC has received honoraria and travel support from Sanofi, up until September 2017.

RD has received speaker honoraria from Biogen Idec, Teva, Neurology Academy, and Sanofi Genzyme. She has received research support from Biogen, Merck, and Celgene.

MD has received personal honoraria for speaking, advisory boards, participation in research and travel expenses from Bayer, Biogen, Celgene (BMS), Merck, Mylan, Novartis, Roche, Sanofi Genzyme, Teva and TG Therapeutics.

SH has received unrestricted educational grants or speaking honoraria from Biogen, Merck Serono, Novartis, Roche, and Sanofi-Aventis.

OP has received honoraria and travel expenses from Biogen, Bayer, Genzyme, Merck, Novartis, Roche, and Teva. He has served on advisory boards for Biogen, Celgene, Novartis, Genzyme, Merck, and Roche.

DR has received consulting fees from Bayer, Celgene, Biogen, Janssen-Cilag, MedDay, Merck Serono, Novartis, Roche, Sanofi Genzyme, and Teva Neuroscience. He has received research support from Actelion, Biogen, GW Pharma, Janssen-Cilag, MedDay, Merck Serono, Mitsubishi, Novartis, Sanofi Genzyme, Teva Neuroscience, and TG Therapeutics.

ET has received consulting or speaker honoraria from Roche, Novartis, and Takeda and travel expenses to attend educational meetings from Biogen, Merck, and Roche.

RdN is the Chair of the NIHR Research for Patient Benefit East Midlands Research Advisory Committee. He has received funding to prepare and deliver lectures on cognitive rehabilitation in multiple sclerosis from Novartis and Biogen.

RN has received support for advisory boards and travel from Novartis, Roche, and Biogen. He has received grant support from the UK MS Society. He is a member of a NICE HTA committee.

NE has served as a member of advisory boards for Biogen, Merck, Novartis, and Roche. He has received grant income from the UK MS Society, MRC, PCORI and NIHR.

CRediT authorship contribution statement

Afagh Garjani: Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rodden M Middleton:** Conceptualization, Data curtion, Investigation, Methodology, Resources, Writing – review & editing. **Rachael Hunter:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Katherine A Tuite-Dalton:** Data curtion, Investigation, Resources, Writing – review & editing. **Alasdair Coles:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Ruth Dobson:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Martin Duddy:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Stella Hughes:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Owen R Pearson:** Conceptualization, Methodology, Supervision, Writing – review & editing. **David Rog:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Emma C Tallantyre:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Roshan das Nair:** Conceptualization, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Richard Nicholas:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Nikos Evangelou:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.102939.

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Appendix 3-B

Your MS and COVID-19 Questionnaire

You had previously reported that you have experienced symptoms of coronavirus infection. In this brief questionnaire, we would like to ask you about your recovery.

- As part of your coronavirus infection, did you experience fever?

    ○ Yes, but I have recovered now

    ○ No

    ○ Yes, and I still have a fever

- At worst, how disabling was your coronavirus infection?

    ○ It was not disabling at all

    ○ I was unwell, but I could look after myself

    ○ I received help for everyday activities even before the infection, and my needs did not change

    ○ I received more help from my family/friends/carer, but I could have done without help

    ○ I needed more help and could not have managed without it

- Most people with MS experience some worsening of their pre-existing MS symptoms during infections such as a cold, flu, or urinary infection. Compared to the last infection you remember before the coronavirus, how did your coronavirus infection affect your pre-existing MS symptoms:

    ○ My MS symptoms were no worse during the coronavirus infection

    ○ My MS symptoms were worse during the coronavirus infection, but it was the same as my last infection

    ○ My MS symptoms were worse during the coronavirus infection, but it was less than my last infection

○ My MS symptoms were worse during the coronavirus infection, and it was worse than my last infection

○ I cannot remember

- Have your pre-existing MS symptoms gone back to how they were before the coronavirus infection?

○ Yes

○ No

If “Yes”: How long did the worsening of your pre-existing MS symptoms last before improving to the state before the coronavirus infection?

○ 1-3 days

○ 4-6 days

○ A week

○ Two weeks

○ Three weeks

○ Four weeks

○ More than four weeks

- Did you experience any new MS symptoms during/since your coronavirus infection that you had not experienced before?

○ Yes

○ No

If “Yes”: What were the new MS symptoms? (Please tick only those symptoms that are new, and you had not experienced before, and please tick all that apply)

□ New weakness

Was this new weakness:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New sensory symptoms (numbness, pins and needles, pain)

Were these new sensory symptoms (numbness, pins and needles, pain)

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New loss of balance

Was this new loss of balance:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New bladder/bowel problems

Were these new Bladder/bowel problems:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New problems with eyesight (blurred vision, double vision)

Were these new problems with eyesight (blurred vision, double vision):

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New fatigue (Not worsening fatigue)

Was this new fatigue (not worsening fatigue):

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New memory problems

Were these new memory problems:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ New mobility problems

Were these new mobility problems:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

□ Other (If your new MS symptom is not list above, please let us know more)

Were these new other MS symptoms:

○ Mild (did not limit my daily activities)

○ Moderate (limited my daily activities, but less than 50%)

○ Severe (limited my daily activities more than 50%)

- Have you recovered from these new MS symptoms?

○ Yes

○ No

- How long did these new MS symptoms go on for?

○ Less than a day

○ 1-3 days

○ 4-6 days

○ A week

○ Two weeks

○ Three weeks

○ Four weeks

○ More than four weeks

- What was the outcome of these new symptoms?

□ Treated with a steroid

□ Admitted to hospital

□ I self-managed

□ Other

Appendix 3-C

Directed Acyclic Graph (DAG)

Chapter 3. COVID-19 Is Associated with MS Exacerbations

The DAG of the COVID-19 and MS Symptoms study were created using DAGitty, a browser-based environment for creating, editing, and analysing DAGs (http://www.dagitty.net/). The DAG model is provided in Figure 3-C.1.

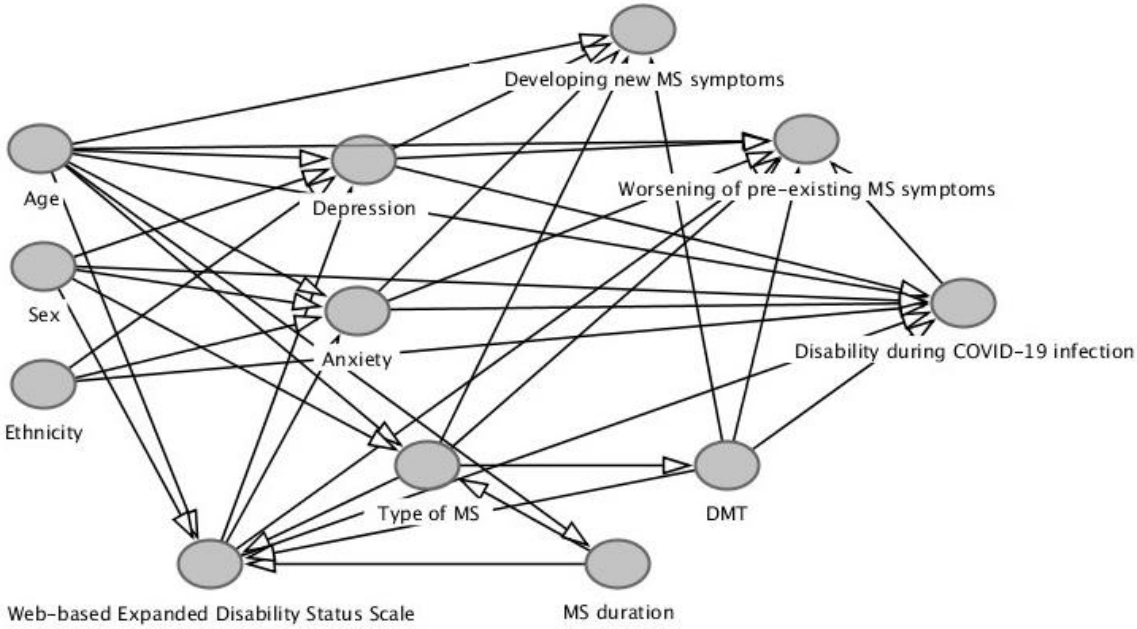

Figure 3-C.1. The directed acyclic graph of the COVID-19 and MS Symptoms study.

The following DAG code can be used to reproduce the model using DAGitty:

```
dag {
bb="0,0,1,1"
"Developing new MS symptoms" [pos="0.551,0.324"]
"Disability during COVID-19 infection" [pos="0.735,0.562"]
"MS duration" [pos="0.536,0.790"]
"Type of MS" [pos="0.427,0.704"]
"Web-based Expanded Disability Status Scale" [pos="0.302,0.791"]
"Worsening of pre-existing MS symptoms" [pos="0.645,0.420"]
Age [pos="0.204,0.428"]
Anxiety [pos="0.386,0.569"]
DMT [pos="0.599,0.704"]
Depression [pos="0.390,0.437"]
```

```
Ethnicity [pos="0.206,0.633"]
Sex [pos="0.206,0.530"]
"Disability during COVID-19 infection" -> "Worsening of pre-existing MS
symptoms"
"MS duration" -> "Type of MS"
"MS duration" -> "Web-based Expanded Disability Status Scale"
"Type of MS" -> "Developing new MS symptoms"
"Type of MS" -> "Web-based Expanded Disability Status Scale"
"Type of MS" -> "Worsening of pre-existing MS symptoms"
"Type of MS" -> DMT
"Web-based Expanded Disability Status Scale" -> "Disability during COVID-19
infection"
"Web-based Expanded Disability Status Scale" -> "Worsening of pre-existing
MS symptoms"
"Web-based Expanded Disability Status Scale" -> Anxiety
"Web-based Expanded Disability Status Scale" -> Depression
Age -> "Developing new MS symptoms"
Age -> "Disability during COVID-19 infection"
Age -> "MS duration"
Age -> "Type of MS"
Age -> "Web-based Expanded Disability Status Scale"
Age -> "Worsening of pre-existing MS symptoms"
Age -> Anxiety
Age -> Depression
Anxiety -> "Developing new MS symptoms"
Anxiety -> "Disability during COVID-19 infection"
Anxiety -> "Worsening of pre-existing MS symptoms"
DMT -> "Developing new MS symptoms"
DMT -> "Disability during COVID-19 infection"
DMT -> "Web-based Expanded Disability Status Scale"
DMT -> "Worsening of pre-existing MS symptoms"
Depression -> "Developing new MS symptoms"
Depression -> "Disability during COVID-19 infection"
Depression -> "Worsening of pre-existing MS symptoms"
Ethnicity -> "Disability during COVID-19 infection"
Ethnicity -> Anxiety
Ethnicity -> Depression
Sex -> "Disability during COVID-19 infection"
Sex -> "Type of MS"
Sex -> "Web-based Expanded Disability Status Scale"
Sex -> Anxiety
Sex -> Depression
}
```

Appendix 4-A

ARTICLE OPEN ACCESS

Recovery From COVID-19 in Multiple Sclerosis

A Prospective and Longitudinal Cohort Study of the United Kingdom Multiple Sclerosis Register

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Abstract

Background and Objectives

To understand the course of recovery from coronavirus disease 2019 (COVID-19) among patients with multiple sclerosis (MS) and to determine its predictors, including patients' pre–COVID-19 physical and mental health status.

Methods

This prospective and longitudinal cohort study recruited patients with MS who reported COVID-19 from March 17, 2020, to March 19, 2021, as part of the United Kingdom MS Register (UKMSR) COVID-19 study. Participants used online questionnaires to regularly update their COVID-19 symptoms, recovery status, and duration of symptoms for those who fully recovered. Questionnaires were date stamped for estimation of COVID-19 symptom duration for those who had not recovered at their last follow-up. The UKMSR holds demographic and up-to-date clinical data on participants as well as their web-based Expanded Disability Status Scale (web-EDSS) and Hospital Anxiety and Depression Scale (HADS) scores. The association between these factors and recovery from COVID-19 was assessed using multivariable Cox regression analysis.

Results

Of the 7,977 patients with MS who participated in the UKMSR COVID-19 study, 599 reported COVID-19 and prospectively updated their recovery status. Twenty-eight hospitalized participants were excluded. At least 165 participants (29.7%) had long-standing COVID-19 symptoms for ≥4 weeks and 69 (12.4%) for ≥12 weeks. Participants with pre–COVID-19 web-EDSS scores ≥7, participants with probable anxiety and/or depression (HADS scores ≥11) before COVID-19 onset, and women were less likely to report recovery from COVID-19.

Discussion

Patients with MS are affected by postacute sequelae of COVID-19. Preexisting severe neurologic impairment or mental health problems appear to increase this risk. These findings can have implications in tailoring their post–COVID-19 rehabilitation.

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Go to Neurology.org/NN for full disclosures. Funding information is provided at the end of the article.

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Glossary

COVID-19 = coronavirus disease 2019; **HADS** = Hospital Anxiety and Depression Scale; **IQR** = interquartile range; **MS** = multiple sclerosis; **PASC** = postacute sequelae of COVID-19; **web-EDSS** = web-based Expanded Disability Status Scale; **UKMSR** = United Kingdom MS Register.

Many patients with multiple sclerosis (MS) evade the serious acute complications of coronavirus disease 2019 (COVID-19), such as hospitalization, respiratory failure, or death.[1,2] Nevertheless, they may still have long-term effects of the infection, known as postacute sequelae of COVID-19 (PASC).

Understanding the burden of PASC among patients with MS and identifying its risk factors will inform MS rehabilitation services, which are going to deal with the emerging needs of patients with MS who had COVID-19. In this study, we aim to understand the course of recovery from COVID-19 in MS and to determine its predictors.

Methods

This prospective and longitudinal cohort study was conducted as part of the United Kingdom MS Register (UKMSR) COVID-19 study.[2] Patients with MS had been reporting whether they had symptoms suggestive of COVID-19 and whether their diagnosis was confirmed by a health care provider or COVID-19 testing, from March 17, 2020—the start of the outbreak in the United Kingdom.[2] Further information about COVID-19 testing was not collected, but, in the United Kingdom, patients with COVID-19 symptoms are only offered a PCR test. Mass COVID-19 testing in the United Kingdom was implemented on May 28, 2020—before then, PCR tests were only available to inpatients. All data were collected using online questionnaires.

Patients with MS with self-reported symptoms suggestive of COVID-19 were included in the study. They were followed up, by email reminders, every 2 weeks to update their COVID-19 symptoms and recovery status until reporting full recovery from COVID-19 symptoms (questions provided in eAppendix 1, links.lww.com/NXI/A670). Participants who reported full recovery also provided the duration of their COVID-19 symptoms. The submitted questionnaires were date stamped for estimation of COVID-19 symptom duration for participants who had not reported full recovery at their last follow-up. Participants were asked to specifically report new or worsened symptoms after their COVID-19.

The UKMSR holds demographic and up-to-date clinical data on registered patients, including comorbidities, MS type, date of MS diagnosis, disease-modifying therapies, web-based Expanded Disability Status Scale (web-EDSS) scores, and Hospital Anxiety and Depression Scale (HADS) scores. The most recent web-EDSS and HADS scores before COVID-19 onset were used.

Participants were grouped into 5 groups based on their web-EDSS score: (1) 0–2.5 (ambulatory without assistance and no or minimal neurologic impairment); (2) 3–3.5 (ambulatory without assistance and moderate neurologic impairment); (3) 4–5.5 (ambulatory without assistance and severe neurologic impairment); (4) 6–6.5 (ambulatory with assistance), and (5) ≥7 (restricted to wheelchair or bed).

HADS is scored (0–21) for anxiety and depression separately. Participants with HADS scores of ≥11 were considered as having probable anxiety or depression.[3] Participants with anxiety, depression, or both were considered as 1 group because these conditions frequently coexist in MS,[4] and the number of participants with anxiety or depression alone was small. Data collected until March 19, 2021, are presented according to STROBE guidelines.[5]

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval for UKMSR studies was obtained from Southwest-Central Bristol Research Ethics Committee (16/SW/0194). All participants provided informed consent online. The study is registered with ClinicalTrials.gov (NCT04354519).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY; 2019).

Continuous variables with normal distribution are presented as mean (SD) and were compared using the independent samples *t* test. Continuous variables without normal distribution and ordinal variables are presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney *U* test. The association between categorical variables was assessed using the χ^2 test or the Fisher exact test. The number of valid values for variables with missing data has been stated.

Univariable and multivariable Cox regression analyses, with time (days) from reporting COVID-19 to full recovery (event) as the dependent variable, were performed to assess the association between demographic and clinical variables and recovery from COVID-19. Participants with persistent symptoms at their last follow-up were censored. A directed acyclic graph was produced (eAppendix 2, links.lww.com/NXI/A670) to identify potential confounding factors, which were subsequently accounted for in the multivariable Cox regression analysis. This method avoids the introduction of bias in the analysis by the erroneous inclusion of colliders and mediators as confounding factors.[6] Listwise deletion was implemented for missing data.

Table 1 Characteristics of Patients With MS and COVID-19 in Relation to the Duration of Their COVID-19 Symptoms

	<4 wk n = 371	≥4 wk[a] n = 165	≥12 wk n = 69
Age, mean (SD), y	49 (11)	50 (11)	51 (11)
Women, no. (%)	275 (74.1)	136 (82.4) *	59 (85.5)*
White ethnicity, no. (%)	350 (94.3)	157 (95.2)	68 (98.6)
Comorbidities[b], no. (%)	n = 295	n = 125	n = 53
Diabetes	12 (4.1)	3 (2.4)	2 (3.8)
Heart disease	6 (2)	1 (0.8)	0 (0)
Hyperlipidemia	21 (7.1)	5 (4)	5 (9.4)
Hypertension	32 (10.8)	13 (10.4)	7 (13.2)
Peripheral vascular disease	1 (0.3)	0 (0)	0 (0)
Kidney disease	3 (1)	3 (2.4)	0 (0)
Liver disease	1 (0.3)	0 (0)	0 (0)
Lung disease	30 (10.2)	18 (14.4)	10 (18.9)
Anxiety and/or depression[c]	80/252 (31.7)	57/113 (50.4) **	25/46 (54.3) *
Web-EDSS score[b], median (IQR)	4 (2.625–6.5) n = 264	5 (3–6.5) n = 113	5.5 (4–6.5) *n = 50
Web-EDSS score = 0–2.5, no. (%)	66 (25)	23 (20.4)	7 (14)
Web-EDSS score = 3–3.5, no. (%)	45 (17)	11 (9.7)	4 (8)
Web-EDSS score = 4–5.5, no. (%)	69 (26.1)	32 (28.3)	15 (30)
Web-EDSS score = 6–6.5, no. (%)	53 (20.1)	31 (27.4)	15 (30)
Web-EDSS score ≥7, no. (%)	31 (11.7)	16 (14.2)	9 (18)
MS disease duration, median (IQR), y	10 (5–17) n = 359	11 (5.25–19) n = 160	13 (6.25–19) n = 68
Type of MS, no. (%)			
RRMS	265 (71.4)	114 (69.1)	48 (69.6)
SPMS	65 (17.5)	33 (20)	15 (21.7)
PPMS	24 (6.5)	10 (6.1)	5 (7.2)
Unknown	17 (4.6)	8 (4.8)	1 (1.4)
Taking a DMT, no. (%)	188 (50.7)	84 (50.9)	32 (46.4)
Alemtuzumab	14 (3.8)	4 (2.4)	2 (2.9)
Beta interferons	31 (8.4)	5 (3)	2 (2.9)
Cladribine	8 (2.2)	3 (1.8)	0 (0)
Dimethyl fumarate	49 (13.2)	25 (15.2)	10 (14.5)
Fingolimod	22 (5.9)	11 (6.7)	3 (4.3)
Glatiramer acetate	16 (4.3)	12 (7.3)	7 (10.1)
Natalizumab	23 (6.2)	10 (6.1)	4 (5.8)
Ocrelizumab	15 (4)	8 (4.8)	3 (4.3)
Rituximab	0 (0)	2 (1.2)	1 (1.4)
Siponimod	1 (0.3)	0 (0)	0 (0)
Teriflunomide	8 (2.2)	3 (1.8)	0 (0)

Continued

Table 1 Characteristics of Patients With MS and COVID-19 in Relation to the Duration of Their COVID-19 Symptoms *(continued)*

	<4 wk n = 371	≥4 wk[a] n = 165	≥12 wk n = 69
Other	1 (0.3)	1 (0.6)	0 (0)

Abbreviations: COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; IQR = interquartile range; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; web-EDSS = web-based Expanded Disability Status Scale.
*$p < 0.05$ and **$p = 0.001$. Comparisons were made to participants with symptom duration of <4 wk.
[a] Includes participants with COVID-19 symptoms for ≥12 weeks.
[b] Before COVID-19 onset.
[c] Participants with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively.

Results are presented as adjusted hazard ratios with 95% confidence intervals.

Data Availability

Data are stored on the UKMSR Secure e-Research Platform at Swansea University Medical School. Line level data cannot be released, but qualified researchers, subject to governance, can request access to data.

Results

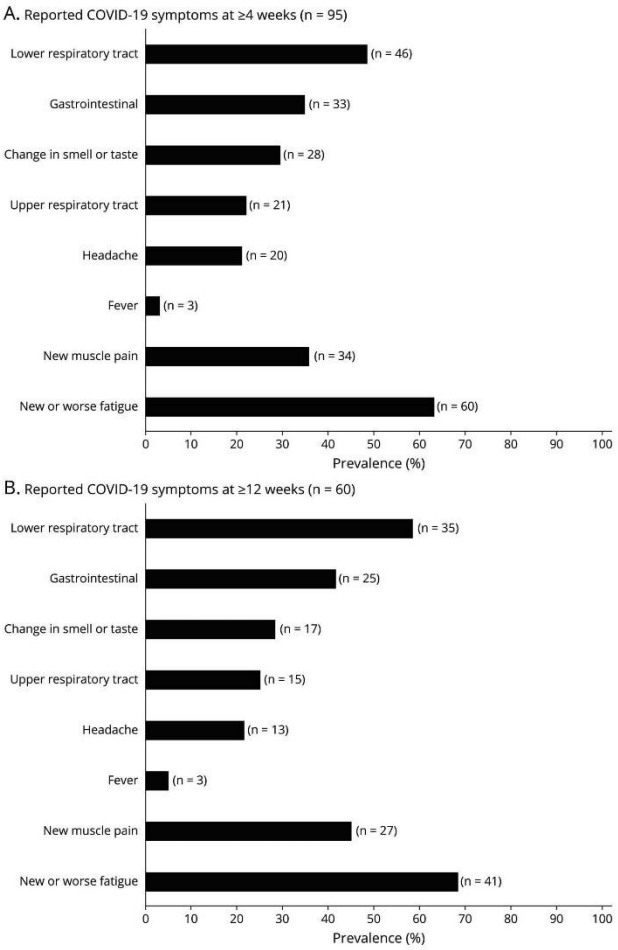
Of the 7,977 patients with MS who participated in the UKMSR COVID-19 study, 1,096 reported COVID-19. A total of 599 patients with MS and COVID-19 updated their recovery status (participants), and 497 did not (nonparticipants). Twenty-eight participants (4.7%) and 8 (1.6%) nonparticipants were hospitalized during their acute infection ($p = 0.05$). Only 16

Table 2 Results of the Multivariable Cox Regression Analysis[a] of Pre–COVID-19 Factors Associated With Recovery From COVID-19

	Included in the analysis, no.	Censored, no.	aHR	Lower 95% CI	Upper 95% CI	Adjustments
Age (1-y increment)	556	115	0.996	0.988	1.005	None
Women vs men	556	115	**0.756**	**0.609**	**0.937**	None
All other ethnicities vs White ethnicity	556	115	1.374	0.937	2.016	None
MS disease duration (1-y increment)	538	112	0.995	0.983	1.008	Age
Anxiety and/or depression[b,c]	314	65	**0.708**	**0.533**	**0.941**	Age, Gender, Ethnicity, Web-EDSS categories
Web-EDSS[c]	380	74	—	—	—	Age, Gender, MS disease duration, MS type
Score = 0–2.5 (reference)	—	—	1	1	1	
Score = 3–3.5	—	—	1.123	0.783	1.610	
Score = 4–5.5	—	—	0.751	0.542	1.040	
Score = 6–6.5	—	—	0.698	0.485	1.006	
Score ≥7	—	—	**0.614**	**0.381**	**0.989**	
MS type	538	112	—	—	—	Age, Gender, MS disease duration
RRMS (reference)	—	—	1	1	1	
SPMS	—	—	1.049	0.765	1.438	
PPMS	—	—	1.212	0.798	1.841	
Taking a DMT	556	115	0.985	0.788	1.232	Age, MS type

Abbreviations: 95% CI = 95% confidence interval; aHR = adjusted hazard ratio; COVID-19 = coronavirus disease 2019; DMT = disease-modifying therapy; MS = multiple sclerosis; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; Web-EDSS = web-based Expanded Disability Status Scale.
Bold indicates statistically significant findings.
[a] Results of the univariable Cox Regression analysis are provided in eTable 2, links.lww.com/NXI/A670.
[b] Participants with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively.
[c] Before COVID-19 onset.

Figure Frequency of COVID-19 Symptoms Among Patients With Multiple Sclerosis With Persistent Symptoms at Their Last Follow-up in ≥4 (A) and ≥12 (B) Weeks From Reporting COVID-19



Gastrointestinal symptoms included diarrhea, nausea or vomiting, or stomach pain. Lower respiratory tract symptoms included coughs, shortness of breath, or heaviness in the chest. Upper respiratory tract symptoms included sore throat, nasal congestion, or sneezing. COVID-19 = coronavirus disease 2019.

participants (and all hospitalized nonparticipants) were admitted to hospital because of COVID-19. Therefore, hospitalized patients with MS were excluded from the analysis. Participants did not differ in their baseline characteristics (including demographics, MS type, web-EDSS score, disease-modifying therapies, comorbidities, or having anxiety and/or depression) from nonparticipants, except for a lower rate of hypertension among participants (10.8%) than nonparticipants (16.3%) (eTable 1, links.lww.com/NXI/A670).

Four hundred forty-four participants (77.8%) reported full recovery from COVID-19 at their last follow-up. Their

median (IQR) symptom duration was 10 (6–21) days (n = 441); 70 recovered in ≥4 weeks and 9 in ≥12 weeks. However, 127 participants (22.2%) had persistent symptoms at their last follow-up. They had been followed up for a median (IQR) of 87 (41–185) days (n = 115), with 95 having symptoms for ≥4 weeks and 60 for ≥12 weeks from reporting COVID-19. Therefore, at least 165 participants (29.7%) had lasting COVID-19 symptoms for ≥4 weeks and 69 (12.4%) for ≥12 weeks. The characteristics of participants by their symptom duration are compared in Table 1. A post hoc analysis among participants with a COVID-19 diagnosis confirmed by a health care provider or testing showed similar findings (eAppendix 3, links.lww.com/NXI/A670).

Participants with a pre–COVID-19 web-EDSS score of ≥7, participants with anxiety and/or depression before COVID-19 onset, and women were less likely to report recovery from COVID-19 (Table 2). Of 95 participants who reported their COVID-19 symptoms at ≥4 weeks, 78 (82.1%) had symptoms, which were not typical for MS (symptoms listed in Figure, except for fatigue and pain). Of 60 participants who reported their symptoms at ≥12 weeks, 50 (83.3%) had non–MS-related symptoms.

Discussion

This prospective study of a large national cohort of nonhospitalized patients with MS and COVID-19 shows that about 30% and 12% of patients experience prolonged COVID-19 symptoms for ≥4 and ≥12 weeks, respectively. These rates in the MS population are higher than the general population, as reported by a study using a similar methodology (13% and 2%, respectively).[7] Another study reports a much higher prevalence of prolonged COVID-19 in the general population, but its retrospective data collection could have led to recall bias.[8] Given that MS shares many neurologic symptoms of COVID-19 and that the infection can lead to MS exacerbations,[9] a high prevalence of long-lasting COVID-19 symptoms in this population may seem expected. More than 80% of patients with MS with persistent COVID-19 symptoms in the study, however, also had symptoms that were not typical for MS. Further studies using direct control groups, from both the general population and patients with MS without COVID-19, are needed to establish the risk of PASC in MS.

An association between physical disability and adverse acute COVID-19 outcomes in MS has been previously reported.[1] This study shows that higher levels of pre–COVID-19 neurologic disability predispose patients with MS to long-term sequelae of COVID-19 as well. Other MS-related factors such as disease duration or disease-modifying therapies did not appear to influence recovery from COVID-19. Patients with MS with pre–COVID-19 mental health problems can also be disproportionately affected by PASC, which has also recently been reported in the general population.[10] The observation that women are more likely to experience prolonged COVID-19 symptoms is in accordance with other studies.[7]

A limitation of the study is that the COVID-19 diagnosis of patients with MS was confirmed by laboratory testing in only a proportion of participants, as widespread testing was not available in the United Kingdom at the time of recruitment. However, the rates of prolonged COVID-19 in the subgroup with confirmed diagnosis and the total study population were similar. Hospitalized patients with MS were excluded to avoid the potential confounding effect of hospitalization on recovery from COVID-19. The association between hospitalization and COVID-19 recovery could not be assessed because of the small sample size of hospitalized patients with MS and the risk of selection bias toward nonhospitalized patients due to the questionnaire-based nature of the study.

These findings will inform MS and post–COVID-19 rehabilitation services in developing individualized pathways for patients with MS, helping to reduce the burden on these health systems in the COVID-19 era. They also highlight the importance of vaccination against COVID-19 in the MS population who appear to be vulnerable to the long-term effects of infection.

Study Funding

United Kingdom Multiple Sclerosis Society (Grant no. 131).

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Appendix *(continued)*

Name	Location	Contribution
Rodden M. Middleton, MBA	Population Data Science, Swansea University Medical School, Swansea, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; and study concept or design
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Nikos Evangelou, FRCP	Mental Health and Clinical Neurosciences Academic Unit, School of Medicine, University of Nottingham, Nottingham, United Kingdom; Clinical Neurology, Nottingham University Hospitals NHS Trust, Nottingham, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

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Appendix 4-B

Follow-up Questions on Recovery from COVID-19

a) Have you recovered from your coronavirus?

- Yes, I have fully recovered.
- I am mostly recovered.
- No, I am still experiencing symptoms.

b) How many days were you affected by the virus?

c) Which of the following symptoms do you still have? (Tick all that apply)

- High temperature
- Coughs
- Breathing difficulties
- Chest tightness
- Sore throat
- Runny nose
- Sneezing
- Headache
- Change of taste or smell
- Feeling queasy or throwing up
- Diarrhoea
- Stomach ache
- New or worse fatigue
- New muscle aches

Appendix 4-C

Directed Acyclic Graph (DAG)

Chapter 4. Recovery From COVID-19 in MS

The DAG in Figure 4-C.1 was used to identify potential confounders for inclusion in the multivariable Cox regression analysis.

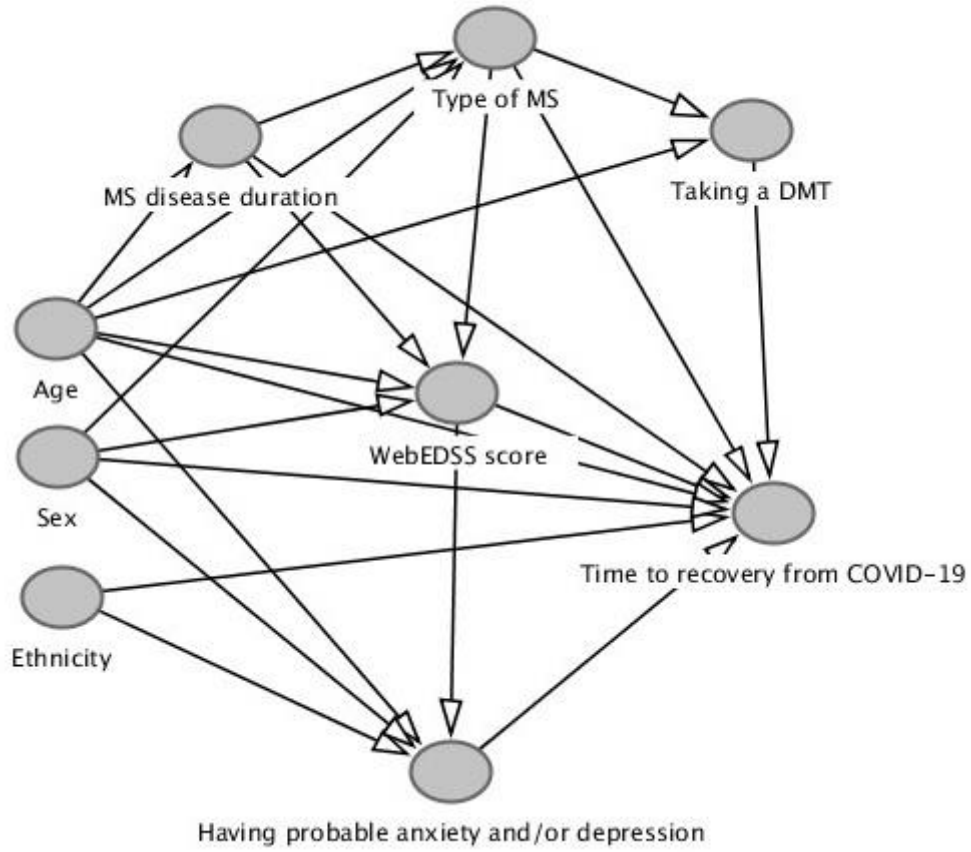

Figure 5-C.1. The directed acyclic graph used for identifying confounders in Chapter 5 of this thesis.

The following code can be used at http://www.dagitty.net/dags.html to replicate the DAG:

```
dag {
bb="0,0,1,1"
"Having probable anxiety and/or depression" [pos="0.283,0.579"]
"MS disease duration" [pos="0.202,0.237"]
"Taking a DMT" [pos="0.389,0.234"]
```

"Time to recovery from COVID-19" [pos="0.397,0.440"]
"Type of MS" [pos="0.299,0.184"]
"WebEDSS score" [pos="0.286,0.376"]
Age [pos="0.144,0.341"]
Ethnicity [pos="0.146,0.485"]
Sex [pos="0.145,0.410"]
"Having probable anxiety and/or depression" -> "Time to recovery from COVID-19"
"MS disease duration" -> "Time to recovery from COVID-19"
"MS disease duration" -> "Type of MS"
"MS disease duration" -> "WebEDSS score"
"Taking a DMT" -> "Time to recovery from COVID-19"
"Type of MS" -> "Taking a DMT"
"Type of MS" -> "Time to recovery from COVID-19"
"Type of MS" -> "WebEDSS score"
"WebEDSS score" -> "Having probable anxiety and/or depression"
"WebEDSS score" -> "Time to recovery from COVID-19"
Age -> "Having probable anxiety and/or depression"
Age -> "MS disease duration"
Age -> "Taking a DMT"
Age -> "Time to recovery from COVID-19"
Age -> "Type of MS"
Age -> "WebEDSS score"
Ethnicity -> "Having probable anxiety and/or depression"
Ethnicity -> "Time to recovery from COVID-19"
Sex -> "Having probable anxiety and/or depression"
Sex -> "Time to recovery from COVID-19"
Sex -> "Type of MS"
Sex -> "WebEDSS score"
}

Appendix 4-D

Table 4-D.1. Results of the univariable Cox regression analysis of pre-COVID-19 factors associated with recovery from COVID-19.

	Included in the analysis no	**Censored** no	**HR**	**Lower 95% CI**	**Upper 95% CI**
Age (1-year increment)	556	115	0.996	0.988	1.005
Women vs men	556	115	**0.756**	**0.609**	**0.937**
All other ethnicities vs White ethnicity	556	115	1.374	0.937	2.016
MS disease duration (1-year increment)	538	112	0.995	0.983	1.008
Anxiety and/or depression [a, b]	314	65	**0.708**	**0.533**	**0.941**
WebEDSS score [b]	380	74	-	-	-
0–2.5 (reference)	-	-	1	1	1
3–3.5	-	-	1.123	0.783	1.610
4–5.5	-	-	0.751	0.542	1.040
6–6.5	-	-	0.698	0.485	1.006
≥ 7	-	-	**0.614**	**0.381**	**0.989**
MS type	538	112	-	-	-
RRMS (reference)	-	-	1	1	1
SPMS	-	-	1.049	0.765	1.438
PPMS	-	-	1.212	0.798	1.841
Taking a DMT	556	115	0.985	0.788	1.232

[a] Participants with Hospital Anxiety and Depression Scale scores ≥11 for anxiety or depression were considered as having probable anxiety or depression, respectively. [b] Prior to COVID-19 onset.

Appendix 5-A

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Original Research Paper

Mental health of people with multiple sclerosis during the COVID-19 outbreak: A prospective cohort and cross-sectional case–control study of the UK MS Register

Multiple Sclerosis Journal
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Abstract

Background: People with MS (pwMS) have had higher rates of anxiety and depression than the general population before the COVID-19 pandemic, placing them at higher risk of experiencing poor psychological wellbeing during the pandemic.

Objective: To assess mental health and its social/lifestyle determinants in pwMS during the first wave of the outbreak in the United Kingdom.

Methods: This is a community-based, prospective longitudinal cohort and cross-sectional case–control online questionnaire study. It includes 2010 pwMS from the UK MS Register and 380 people without MS.

Results: The Hospital Anxiety and Depression Scale scores of pwMS for anxiety and depression during the outbreak did not change from the previous year. PwMS were more likely to have anxiety (using General Anxiety Disorder-7) and/or depression (using Patient Health Questionnaire-9) than controls during the outbreak (OR: 2.14, 95% CI: 1.58–2.91). PwMS felt lonelier (OR: 1.37, 95% CI: 1.04–1.80) reported worse social support (OR: 1.90, 95% CI: 1.18–3.07) and reported worsened exercise habits (OR: 1.65, 95% CI: 1.18–2.32) during the outbreak than controls.

Conclusion: Early in the pandemic, pwMS remained at higher risk of experiencing anxiety and depression than the general population. It is important that multidisciplinary teams improve their support for the wellbeing of pwMS, who are vulnerable to the negative effects of the pandemic on their lifestyle and social support.

Keywords: Multiple sclerosis, COVID-19, mental health, social, lifestyle

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Introduction

The coronavirus disease-2019 (COVID-19) pandemic transformed the lives of people in unpredictable ways and posed a risk to their mental wellbeing.[1] Early in the pandemic, the UK general population experienced higher levels of psychological distress compared to the pre-COVID-19 era.[2] Consequently, research on mental health effects of the pandemic across vulnerable groups became a multidisciplinary research priority.[3]

At the start of the outbreak, anecdotal evidence suggested considerable fear of COVID-19 among people with multiple sclerosis (pwMS) because of their long-term physical disabilities and the immunosuppression caused by some disease-modifying therapies (DMTs). The assessment of anxiety and depression in pwMS was specifically warranted because pwMS were known to have higher pre-COVID-19 rates of anxiety and depression than the general population.[4,5] Furthermore, similar to the general population,

changes in lifestyle and social factors could influence the mental health of pwMS.[5–8]

Therefore, we aimed to assess the following:

1. Mental health, its lifestyle and social determinants, and its association with general health among pwMS during the outbreak and compare them to people without MS.
2. Levels of anxiety and depression among pwMS before and after the outbreak.

Patients and methods

Study design, setting and participants

The MS-COVID-19 study is an ongoing community-based, prospective and longitudinal cohort study conducted as part of the UK MS Register (UKMSR) (clinicaltrials.gov: NCT04354519).[9] The UKMSR has been collecting patient-reported data from pwMS since 2011.[10] For the MS-COVID-19 study, we have been collecting COVID-19 related data from pwMS using online self-administered questionnaires since 17 March 2020 – the beginning of the COVID-19 outbreak in the United Kingdom.

On 22 May 2020, we invited pwMS registered with the UKMSR (including pwMS who were taking part in the MS-COVID-19 study) by email to complete questionnaires about their mental health, its social and lifestyle determinants, and their general health on a one-off basis (Supplementary Material). In addition, we provided them with a link to invite people without MS ('controls') to complete these same questionnaires, adding a case–control component to the study. PwMS and controls who responded to at least one of the questionnaires were included in the study (i.e. participants of the mental health study). The study flow diagram is depicted in Figure 1.

In this paper, we report cross-sectional findings on the mental health of pwMS, its determinants, and their general health during the outbreak (22 May 2020 to 16 July 2020) and compare them to controls. We also report longitudinal findings on anxiety and depression levels of pwMS pre-COVID-19 (28 February to 1 April 2019 and 3 September to 1 October 2019) and post-COVID-19 (7 February to 12 May 2020). We report the study according to the STROBE guidelines.

Ethical approval and consent

Ethical approval for UKMSR studies was obtained from South West-Central Bristol Research Ethics Committee (16/SW/0194). The case–control study received separate ethical approval from the Departmental Ethics Committee (4913-4902). Participants provided informed consent online.

Data collection

The UKMSR data. The UKMSR holds demographic data (age, gender, ethnicity), clinical data (type of MS, MS disease duration from diagnosis, DMTs), web-based Expanded Disability Status Scale (webEDSS) scores[11] and Hospital Anxiety and Depression Scale scores of registered pwMS.[12] We used the last webEDSS scores collected from 9 February 2017 to 3 August 2020 to measure physical disability in pwMS. We used HADS scores for anxiety (HADS-A) and depression (HADS-D) among pwMS to compare their anxiety and depression levels during the outbreak to the year before. We considered a HADS score ≥ 11 as probable caseness of anxiety or depression (referred to as *having HADS-anxiety or HADS-depression*, here).[13] HADS scores for controls were not available.

The MS-COVID-19 study data. In the MS-COVID-19 study, we asked pwMS whether they were self-isolating and whether they had symptoms suggestive of a diagnosis of COVID-19.[9] These data were not available for controls.

Mental health questionnaires. We used the General Anxiety Disorder 7-item (GAD-7) and Patient Health Questionnaire 9-question (PHQ-9) scales to assess anxiety and depression, respectively, among pwMS and controls during the outbreak.[14,15] We used a cut-off ≥ 10 for probable caseness of anxiety or depression (referred to as *having anxiety or depression*, here).[13]

We used the Impact of Event Scale–Revised (IES-R) to assess symptoms of post-traumatic stress disorder (PTSD) in pwMS and controls during the outbreak.[16] We considered scores ≥ 33 as probable caseness of PTSD (referred to as *having PTSD*, here).[16] We considered the IES-R subscales, including avoidance, hyperarousal, and intrusion in the analysis.[16]

To measure optimism during the outbreak, we used the Revised Life Orientation Test (LOT-R) scale with higher scores indicating more optimism.[17]

Social and lifestyle determinants of mental health questionnaires. We developed a questionnaire to assess whether participants had any changes (better/worse) in their lives related to social (relationships,

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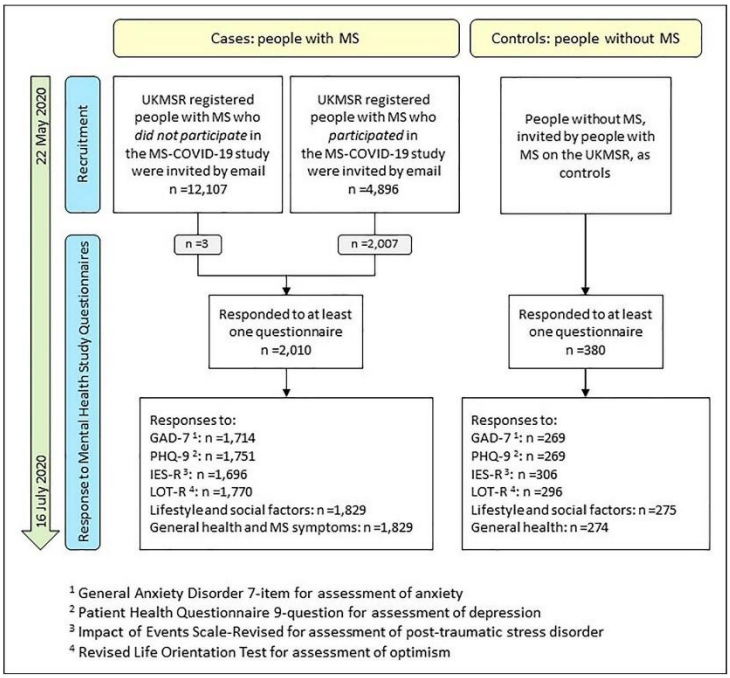

Figure 1. Flow diagram of the MS-COVID-19 mental health study of the UKMSR.

social support, work, feeling of loneliness) and lifestyle (exercise, diet, smoking and alcohol intake) factors during the outbreak compared to the year before. Participants used a visual analogue scale to indicate the change, with 'no change' in the middle (45–55), 'better' to the right (56–100) and 'worse' to the left (0–44).

General health and MS symptoms questionnaires. We asked participants to report how their general health and (only for pwMS) MS symptoms had changed during the outbreak compared to the year before. We developed a similar questionnaire as described above.

Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA; 2017) and R (R Core Team, 2019).

Cross-sectional analysis. Continuous variables were assessed for normality of distribution by visual inspection of data. Data were analysed using the Mann–Whitney U-test and presented as median (interquartile range (IQR)) when not normally distributed and using the *t*-test and presented as mean (standard deviation (SD)) when normally distributed. The Mann–Whitney U-test was also used for assessing ordinal variables. To assess the association between categorical variables, the chi-square test was used (Fisher's exact test when expected count ≤ 5).

For comparisons between pwMS and controls, multivariable logistic regression analysis was used – binomial or multinomial, based on the dependent variable. To ascertain the association between mental health variables or having had COVID-19 and changes in general health or MS symptoms, multivariable multinomial logistic regression analysis was used. In

Table 1. Demographic and clinical characteristics of participants and non-participants (from the total UKMSR population) of the MS and COVID-19 mental health study.

	Participants[a]		Non-participants[a]
	People with MS, $n=2010$	Controls, $n=380$	People with MS, $n=17,003$
Age in years, median (IQR)	56 (48–63), $n=2006$	49 (37–61)[b], $n=340$	53 (44–62)[b], $n=14,993$
Women, *n* (%)	1488 (74.3)	248 (73.6)	11,089 (74.0)
White ethnicity, *n* (%)	1942 (81.8)	329 (97.1)	13,240 (96)
Smoker[c], *n* (%)	160 (8.7)	20 (7.2)	409 (23.8)[b]
Alcohol intake[c], *n* (%)	1141 (62.4)	216 (77.7)[b]	NA
MS-related factors			
RRMS: PMS, *n*	1114: 781	NA	7031: 4475
MS disease duration in years, median (IQR)	12 (6–20), $n=1975$	NA	12 (7–20), $n=13,094$
Taking DMTs, *n* (%)	862 (42.9)	NA	2034 (51.1)[b]
webEDSS, median (IQR)	5.5 (3–6.5), $n=1679$	NA	5.5 (3–6.5), $n=5628$
HADS-A score[c], median (IQR)	6 (3–9), $n=1350$	NA	7 (3–10)[b], $n=1553$
With anxiety[c,d], *n* (%)	251 (18.6)	NA	369 (23.8)[e]
HADS-D score[c], median (IQR)	6 (3–10), $n=1350$	NA	6 (3–10), $n=1553$
With depression[c,d], *n* (%)	282 (20.9)	NA	328 (21.1)
With anxiety and/or depression[c,d], *n* (%)	385 (28.5)	NA	496 (31.9)

COVID-19: coronavirus disease 2019; HADS: Hospital Anxiety and Depression Scale (HADS-A for anxiety and HADS-D for depression); MS: multiple sclerosis; RRMS: relapsing-remitting MS; PMS: progressive MS (includes primary and secondary progressive types of MS); DMTs: disease-modifying therapies; NA: not applicable or not available; UKMSR: UK MS Register; webEDSS: web-based Expanded Disability Status Scale.
[a]Participants with missing data have been excluded from the analysis for each variable separately.
[b]*p*-value compared to people with MS (participants) <0.001.
[c]Before the COVID-19 outbreak.
[d]HADS score $\geqslant 11$ was considered as probable caseness of anxiety or depression.
[e]*p*-value compared to people with MS (participants) $=0.001$.

each regression analysis, no change in the outcome was set as the reference value.

Directed acyclic graphs (DAGs) were built to determine potential confounding factors for individual regression analyses (Supplementary Material).[18] A separate DAG was used for each exposure and outcome analysis model.[18] We chose this approach to avoid introducing bias by controlling for colliders and mediators in the regression analyses models which is a common issue in psychological research.[19] Confounding factors controlled for in each analysis have been stated in the results, and where not mentioned, adjustments for age, gender, and ethnicity were made. Listwise deletion was implemented for missing data. The number of cases included in each regression analysis has been indicated where there was missing data. The results of the regression analyses are presented as odds ratio (OR) and 95% confidence intervals (CIs).

Longitudinal analysis. The HADS scores of pwMS before and during the outbreak were compared using the Mann–Whitney U-test (paired). The proportion of pwMS with HADS-anxiety or HADS-depression before and during the outbreak were compared using the McNemar's test.

Results

Participants

A total of 2010 pwMS and 380 controls were included in the study (Figure 1). Characteristics of pwMS (participants and non-participants from the total UKMSR population) and controls are presented in Table 1. A total of 2226 pwMS on the UKMSR had provided a HADS score both during and before the outbreak (1165 were participants of the mental health study).

Anxiety, depression and PTSD

Mental health characteristics of pwMS and controls are presented in Table 2.

PwMS were more likely to have anxiety and/or depression during the outbreak than controls ($n=1982$; OR: 2.14, 95% CI: 1.57–2.91). The likelihood of having

Table 2. Mental health characteristics of participants of the MS-COVID-19 mental health study during the COVID-19 outbreak.

	People with MS	Controls	*p*-value
GAD-7, median (IQR)	4 (1–8), *n*=1714	4 (1–7), *n*=269	0.81
With anxiety[a], *n* (%)	334 (19.5)	45 (16.7)	0.29
PHQ-9, median (IQR)	6 (3–12), *n*=1751	5 (2–9), *n*=269	0.002
With depression[a], *n* (%)	573 (32.7)	64 (23.8)	0.003
With anxiety and/or depression[a], *n* (%)	632 (36.8), *n*=1781	73 (27.1), *n*=269	0.002
IES-R, median (IQR)	16 (6–32), *n*=1696	20 (10–33), *n*=306	0.01
With symptoms of PTSD[a], *n* (%)	398 (23.5)	77 (25.2)	0.52
IES-R subscales, median (IQR)			
Avoidance (scored 0–32)	7 (2–13), *n*=1790	8 (4–13), *n*=307	0.06
Hyperarousal (scored 0–24)	4 (1–8), *n*=1797	4.5 (1–9), *n*=306	0.06
Intrusion (scored 0–32)	5 (1–11), *n*=1797	7 (3–12), *n*=307	0.001
LOT-R, median (IQR) (scored 0–24)	12 (10–13), *n*=1770	14 (10–18), *n*=296	< 0.001

COVID-19: coronavirus disease 2019; MS: multiple sclerosis; GAD-7: General Anxiety Disorder 7-item; PHQ-9: Patient Health Questionnaire 9-questions; IES-R: Impact of Event Scale–Revised; PTSD: post-traumatic stress disorder; LOT-R: Revised Life Orientation Test.
[a]GAD-7 ⩾ 10 (scored 0–21), PHQ-9 ⩾ 10 (scored 0–27) and IES-R ⩾ 33 (scored 0–88) are regarded as experiencing symptoms indicative of a probable case of anxiety, depression and PTSD, respectively.

Table 3. HADS-A and HADS-D scores (scored 0–21) of people with MS during the COVID-19 outbreak and the year before the outbreak.

	During the outbreak vs anytime the year before			During the outbreak vs same period the year before		
	Before[a]	During[b]	*p*-value	Before[c]	During[b]	*p*-value
Registered with the UKMSR	*n*=2226			*n*=336		
HADS-A, median (IQR)	6 (3–10)	6 (3–10)	0.87	7 (3–10)	7 (3–10)	0.91
With anxiety[d], *n* (%)	463 (20.8)	470 (21.1)	0.72	77 (22.9)	81 (24.1)	0.69
HADS-D, median (IQR)	6 (3–10)	7 (3–10)	0.23	7 (4–10)	7 (4–10)	0.68
With depression[d], *n* (%)	470 (21.1)	475 (21.3)	0.81	79 (23.5)	69 (20.5)	0.20
With anxiety and/or depression[d], *n* (%)	660 (29.6)	658 (29.6)	0.96	110 (32.7)	106 (31.5)	0.72
Participants of the mental health study	*n*=1165			*n*=114		
HADS-A, mean (SD)	6 (3–9)	6 (3–9)	0.49	6 (2–9)	6 (3–9)	0.63
with anxiety[d], *n* (%)	207 (17.8)	214 (18.4)	0.61	17 (14.9)	23 (20.2)	0.24
HADS-D, mean (SD)	6 (3–10)	6 (3–10)	0.63	7 (3.75–10)	7 (4–10)	0.89
with depression, *n* (%)	235 (20.2)	246 (21.1)	0.39	23 (20.2)	22 (19.3)	1
With anxiety and/or depression[d], *n* (%)	317 (27.2)	324 (27.8)	0.65	30 (26.3)	31 (27.2)	1

COVID-19: coronavirus disease 2019; HADS: Hospital Anxiety and Depression Scale; MS: multiple sclerosis; HADS-A: HADS for anxiety; HADS-D: HADS for depression; UKMSR: UK MS Register.
[a]Most recent response from 28 February to 1 April 2019 or 3 September to 1 October 2019.
[b]Most recent response from 7 February to 12 May 2020.
[c]Most recent response from 28 February to 1 April 2019.
[d]HADS score ⩾ 11 was considered as probable caseness of anxiety or depression.

PTSD in pwMS during the outbreak was not different from controls (*n*=1996; OR: 1.13, 95% CI: 0.84–1.52).

The HADS scores of pwMS during the outbreak had not significantly changed from their last score the year before (Table 3).

Having had COVID-19 was not associated with having anxiety and/or depression during the outbreak (after the infection, if present) (OR: 1.43, 95% CI: 0.75–2.74) (*n*=1128; adjusted for age, gender, ethnicity, webEDSS, self-isolation, taking DMTs, and HADS-anxiety and/or HADS-depression before the outbreak). HADS-anxiety and/or HADS-depression

Table 4. Changes in general health and MS symptoms during the COVID-19 outbreak compared to before the outbreak.

	People with MS, *n* (%)	Controls, *n* (%)	*p*-value[a]
Changes in general health			
No change	863 (47.2)	142 (51.8)	< 0.001
Worse	754 (40.7)	74 (27)	
Better	221 (12.1)	58 (21.2)	
Changes in MS symptoms			
No change	979 (53.5)	NA	NA
Worse	758 (41.4)	NA	
Better	92 (5)	NA	

COVID-19: coronavirus disease 2019; MS: multiple sclerosis.
[a]Chi-square test.

before the outbreak did not predict self-reporting COVID-19 among pwMS (OR: 1.04, 95% CI: 0.73–1.48) ($n=2655$; adjusted for age, gender, webEDSS and taking DMTs).

General health and MS symptoms

A total of 1829 pwMS and 274 controls responded to the change in general health question, and 1829 pwMS responded to the change in MS symptoms question (Table 4).

PwMS were more likely than controls to report a decline in their general health during the outbreak compared to before (OR: 1.95, 95% CI: 1.43–2.65). In a *post hoc* analysis, we compared this outcome (decline in general health) between pwMS and controls separately within two groups: (1) participants *with* anxiety and/or depression and (2) participants *without* anxiety or depression. Among participants *without* anxiety or depression ($n=1263$), the findings were similar: pwMS had a higher likelihood of a decline in general health than controls (OR: 1.79, 95% CI: 1.16–2.76). However, among participants *with* anxiety or depression ($n=673$), there was no difference between pwMS and controls in reporting a decline in general health (OR: 1.51, 95% CI: 0.86–2.65).

Among only pwMS, the general health of participants with anxiety and/or depression during the outbreak was more likely to deteriorate than those without anxiety or depression (OR: 3.59, 95% CI: 2.71–4.76) ($n=1398$; adjusted for age, webEDSS, self-diagnosed COVID-19, LOT-R and changes in loneliness).

PwMS with COVID-19 were more likely to report deterioration in their general health than those without COVID-19 (OR: 1.99, 95% CI: 1.07–3.69) ($n=1055$; adjusted for age, gender, ethnicity, webEDSS, taking DMTs, self-isolation, and changes in HADS-A and HADS-D from before the outbreak).

PwMS with anxiety and/or depression during the outbreak were more likely to report worsening of their MS symptoms compared to those without anxiety or depression (OR: 5.23, 95% CI: 4.16–6.57) ($n=1611$; adjusted for taking DMTs, MS type, COVID-19 and LOT-R).

Having had COVID-19 predicted a higher likelihood of MS symptoms worsening (OR: 1.97, 95% CI: 1.06–3.67) ($n=1052$; adjusted for age, gender, ethnicity, webEDSS, taking DMTs, self-isolation, and changes in HADS-A and HADS-D from before the outbreak).

Social and lifestyle determinants of mental health during the outbreak

Changes in social and lifestyle factors of pwMS and controls during the outbreak are presented in Table 5.

PwMS were more likely to feel lonelier than controls (OR: 1.36, 95% CI: 1.04–1.80). Among pwMS *with* anxiety and/or depression during the outbreak, 73.3% ($n=442$) reported feeling lonelier as opposed to 31.5% ($n=340$) of those *without* anxiety or depression ($p<0.001$). The findings were similar among pwMS with and without HADS-anxiety and/or HADS-depression before the outbreak (60.5% ($n=214$) vs 37.2% ($n=336$) felt lonelier, $p<0.001$).

PwMS were more likely to experience worsening of their social support than controls (OR: 1.90, 95% CI: 1.18–3.07). A larger proportion of pwMS with anxiety and/or depression during the outbreak reported worsening of their social support than those without anxiety or depression (23.9% ($n=144$) vs 9.5% ($n=103$) $p<0.001$) – similar to those with and without HADS-anxiety and/or HADS-depression before the outbreak (24% ($n=85$) vs 11% ($n=99$) $p<0.001$). The likelihood of experiencing worse relationships during the outbreak among pwMS was not significantly different from controls (OR: 1.35, 95% CI: 0.93–1.96), but pwMS were less likely to report having better relationships compared to before the outbreak (OR: 0.65, 95% CI: 0.48–0.88).

The exercise habits of pwMS were more likely to become worse than controls (OR: 1.65, 95% CI:

Table 5. Changes in social and lifestyle determinants of mental health during the COVID-19 outbreak compared to before the outbreak.

	People with MS, *n* (%)	Controls, *n* (%)	*p*-value[a]
Change in relationships			
The same	1042 (57)	133 (48.7)	< 0.001
Worse	393 (21.5)	45 (16.5)	
Better	394 (21.5)	95 (34.8)	
Change in social support			
The same	821 (44.9)	122 (44.5)	0.01
Worse	265 (14.5)	23 (8.4)	
Better	743 (40.6)	129 (47.1)	
Change in loneliness			
The same	857 (46.9)	138 (50.5)	0.51
Feeling lonelier	843 (46.1)	118 (43.2)	
Feeling less lonely	129 (7.1)	17 (6.2)	
Change in work			
Yes	372 (20.3)	81 (29.5)	0.001
No	1457 (79.7)	194 (70.5)	
Change in income			
The same	1087 (59.4)	164 (59.9)	0.88
Less	582 (31.8)	84 (30.7)	
More	160 (8.7)	26 (9.5)	
Change in exercise			
The same	538 (29.4)	81 (29.6)	< 0.001
Worse	766 (41.9)	80 (29.2)	
Better	525 (28.7)	113 (41.2)	
Change in diet			
The same	750 (41)	82 (30)	< 0.001
Worse	704 (38.5)	108 (39.6)	
Better	375 (20.5)	80 (30.4)	
Change in smoking			
The same	55 (34.4)	9 (45)	0.54[b]
More	30 (18.8)	2 (10)	
Less	75 (46.9)	9 (45)	
Change in alcohol intake			
The same	550 (48.2)	78 (36.4)	< 0.001
More	244 (21.4)	29 (13.6)	
Less	347 (30.4)	107 (50)	

COVID-19: coronavirus disease 2019; MS: multiple sclerosis.
[a]Chi-square test.
[b]Fisher's exact test.

1.18–2.32). Among pwMS, HADS-anxiety and/or HADS-depression before the outbreak was associated with worsening of exercise during the outbreak (OR: 1.38, 95% CI: 1.03–1.86). A higher webEDSS score among pwMS was not significantly associated with worsening of exercise (OR: 1.03, 95% CI: 0.96–1.11), but predicted a lower likelihood of having better exercise during the outbreak than before (OR: 0.77, 95% CI: 0.71–0.84) (n=1541; adjusted for age, gender, taking DMTs, and MS type). Controls were more likely to have improved their diet than pwMS during the outbreak (OR: 1.64, 95% CI: 1.16–2.32).

PwMS were not significantly different from controls in terms of having undergone a change in their work (OR: 0.80, 95% CI: 0.59–1.08). A higher webEDSS score predicted a lower likelihood of undergoing a change in work among pwMS (OR: 0.86, 95% CI:

0.80–0.92) (n=1541; adjusted for age, gender, MS type and taking DMTs). Among participants whose work had changed, pwMS were more likely to report being more stressed by this change than controls (OR: 2.40, 95% CI: 1.12–5.18). PwMS with and without anxiety and/or depression during the outbreak were not significantly different in feeling more stressed due to a change in work (OR: 1.29, 95% CI: 0.64–2.60). The absence of anxiety and depression among pwMS, however, was associated with a higher likelihood of feeling less stressed due to a change in work (OR: 3.64, 95% CI: 1.95–6.80) (n=347; adjusted for changes in support, relationships and income).

Compared to controls, pwMS were more likely to experience a reduction in their income during the outbreak (OR: 1.41, 95% CI: 1.04–1.90). Among participants who underwent a change in work, there was no significant difference between pwMS and controls in having a reduction (OR: 1.09, 95% CI: 0.63–1.88) or increase in income (OR: 0.89, 95% CI: 0.39–2.06).

Discussion

Our findings add to the evidence that pwMS are more likely to experience anxiety and depression than the general population.[4,5] This study on a large national population of pwMS covers the first lockdown in the United Kingdom, which started on 23 March 2020 and was eased on 4 July 2020. We did not find a significant change in the levels of anxiety and depression among pwMS during this period compared to the year before, which is consistent with the results of other studies.[20–22] Taken together, these findings suggest that the differences we, and others,[22,23] have found in anxiety and depression between pwMS and those without MS during the outbreak were most likely due to MS-related factors rather than the outbreak at the early phases of the pandemic. Studies of the general population have shown that levels of psychological distress have increased during the pandemic and people with higher risk of COVID-19, young adults, women and populations with pre-existing mental or physical health conditions have fared even worse.[2,24] Given that pwMS meet one or more of these conditions, we have considered why their anxiety and depression levels have not changed in line with general population surveys. One reason could be because pwMS are resilient,[20] or because support systems were already in place for pwMS and these were agilely mobilised to address the concerns of this population quickly when the pandemic started (e.g. the local branches of the UK MS Society, which has peer-support groups and had a helpline that was available for pwMS).[25] More than 85% of pwMS in our study reported that the social support they received before the outbreak had improved or had not changed during the outbreak. We do not know whether the pandemic will have a more profound effect on pwMS in the future. Studies should continue to monitor the mental wellbeing of pwMS throughout the pandemic and thereafter.

Poor mental health has a negative impact on the quality of life, and physical and cognitive function of pwMS.[26] The study found that anxiety and depression have a substantial negative effect on the general health of pwMS and their MS symptoms, which can be greater than the impact of COVID-19. This points to a need for MS services to provide continued targeted multidisciplinary psychological support for this population.

We found that many pwMS were feeling lonelier during the outbreak than before and they were more likely to feel this way if they had anxiety or depression. PwMS were slightly more likely than people without MS to feel lonelier during the outbreak. The observations that loneliness is linked with poor health-related outcomes and depression,[27–29] along with our findings, point to a need to address loneliness among pwMS during periods of lockdown. Interventions for homebound older adults, that improve social connectedness and reduce depressive symptoms and disability,[30] could be adapted for pwMS.

Many pwMS did not experience any changes in their social support, relationships, work or income after the outbreak, suggesting that the response of the MS community to the unforeseen transformations at the early stages of the pandemic was effective. The lockdown also had potential benefits to pwMS which have been pointed out by other authors.[20] However, when there was a change in these social factors, pwMS were affected more adversely than those without MS.

The restrictions imposed by the pandemic limited the physical activity of pwMS and did not provide them the opportunity to develop better diets compared to people without MS. Therefore, pwMS appear to be more susceptible to the adverse effects of the outbreak on lifestyle. These are important aspects for clinicians to assess and address in routine encounters because improving lifestyle factors (such as exercise) can improve the mental and physical health of pwMS.[31,32]

Our results confirm that anxiety and depression in pwMS are not specific to the COVID-19 era: they have remained high before and during the pandemic.

Social and lifestyle factors have an undeniable role in mental health,[5–8] but these factors changed in different directions among our study population of pwMS (e.g. some felt lonelier while others received better social support during the outbreak) which could have resulted in the stable anxiety and depression levels observed among pwMS.

It is not uncommon for mental health conditions to go undetected.[33] There is scope for effective management of anxiety and depression in pwMS, and modifications in lifestyle and social factors may provide additional benefits to their health-related quality of life.[34,35] Therefore, it is vital that clinicians routinely screen for mental health problems, particularly in this COVID-19 era, and refer pwMS to appropriate well-being or mental health services for further assessment and support. It is also important that the MS community is aware of their specific vulnerabilities, so that they can take steps to proactively seek support.

Limitations of the study

We cannot precisely calculate our response rate (in pwMS and controls) as we do not know how many people received the study emails. This is a common limitation in studies that recruit participants through registries or social media.[24] We tried to increase our recruitment by advertising the study and sending reminder emails.[36] Nevertheless, we have studied a large national population of pwMS- the largest among current COVID-19 and mental health studies among pwMS.

The mental health study MS sample had slightly lower levels of anxiety than non-participants from the UKMSR and, therefore, their response to the pandemic could have been different. Nevertheless, our findings are in keeping with the results of similar studies.[20–22]

Different cut-offs have been recommended to identify caseness of anxiety and depression using HADS.[37] Here, we used a-priori cut-offs based on a validation study in MS.[13]

Failure to find a difference between HADS scores before and during the outbreak might be influenced by seasonal effects on experiencing anxiety and depression symptoms. Changes in HADS score could not be tested for each season in 2019 and 2020 separately because of small sample sizes.

The UKMSR was not collecting data on social and lifestyle determinants of mental health (as assessed in this study) before the COVID-19 outbreak. Therefore, we were unable to directly compare these factors during and before the outbreak. We tried to overcome this problem by asking participants about *changes* in these factors during the COVID-19 outbreak compared to before.

We asked pwMS to invite people without MS ('controls') to the study who could be their friends and relatives, sharing similar social networks or living in similar neighbourhoods with similar socioeconomic status. This can be a strength in that the controls and pwMS are similar but could also lessen the actual difference between their mental health status. However, the proportion of controls who had anxiety and/or depression in our study (27.1%) is comparable to findings among the UK general population during the same period (27.3%).[2]

We included self-reported COVID-19 instead of confirmed cases since the sample size for the latter was small. However, pwMS with anxiety and/or depression did not tend to report having had COVID-19 any more than pwMS without anxiety or depression.

We could not study the association between ethnicity and mental health because the number of people from ethnic backgrounds other than White ethnicity in the UKMSR was small.

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Author contributions

R.d.N., R.H., N.E. and R.N. conceived the idea of the study. R.d.N., R.H., A.G., R.M.M., K.A.T.-D., N.E. and R.N. were involved in the design and execution of the study including data collection. Data were collected through the UK MS Register (UKMSR) with support from R.M.M., K.A.T.-D. and D.V.F. A.G. carried out pooling of the data with support from R.M.M. A.G. performed the data analysis with support from

G.R.L. The manuscript was drafted by A.G. and R.d.N., revised by R.M., R.H., N.E., R.N. and G.R.L., with intellectual contributions from all authors.

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Supplemental material

Supplemental material for this article is available online.

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Appendix 5-B

UK MS Register Covid-19 Sub Study: Life during the Pandemic

We would like to understand how your life has been affected by the COVID-19 pandemic. There are only 12 questions, and it should take approximately 4 minutes to complete.

You will see a slider for each question. You will notice that the slider represents a number between 0 and 100. Using your mouse (or finger if you are on a tablet or mobile phone) please move the slider to where on the scale best describes your situation, between 0 and 100. If there is no change, just click the slider once and it will change to dark blue.

The stress or pressure of the COVID-19 pandemic has made my MS symptoms...

Worse — No change — Better

(Place a mark on the scale above)

Since the COVID-19 pandemic the household income has changed and is now...

Worse — No change — Better

(Place a mark on the scale above)

Since the COVID-19 pandemic, my personal relationships at home have changed and ar

No change — Better

(Place a mark on the scale above)

Since the COVID-19 pandemic, my diet is ...

No change — Better

(Place a mark on the scale above)

Since the COVID-19 pandemic, my feelings of loneliness have become...

Worse — No change — Better

(Place a mark on the scale above)

How would you rate your overall health today...it has become....

Worse — No change — Better

(Place a mark on the scale above)

Since the COVID-19 pandemic, my work/occupation has changed

◯ Yes ◯ No

Since the change in my occupation/work situation, I stress ..

Less — No change — More

(Place a mark on the scale above)

Since the COVID-19 pandemic, the support I've received from family, friends, and neighbours has been...

Less — No change — More

(Place a mark on the scale above)

Since the COVID-19 pandemic, I exercise

Less — No change — More

(Place a mark on the scale above)

Please let us know if you drink alcohol

◯ Yes ◯ No

Since the COVID-19 pandemic, I drink alcohol...

Less — No change — More

(Place a mark on the scale above)

Please let us know if you smoke

◯ Yes ◯ No

Since the COVID-19 pandemic, I smoke...

Less — No change — More

(Place a mark on the scale above)

Appendix 5-C

Directed Acyclic Graph (DAG)

Chapter 5. Mental Health of people with MS During the COVID-19 Outbreak

The DAGs of the COVID-19-MS Mental Health study were created using DAGitty, a browser-based environment for creating, editing, and analysing DAGs (http://www.dagitty.net). The DAGs and their codes have been provided below (Figures 5-C.1 and 5-C.2).

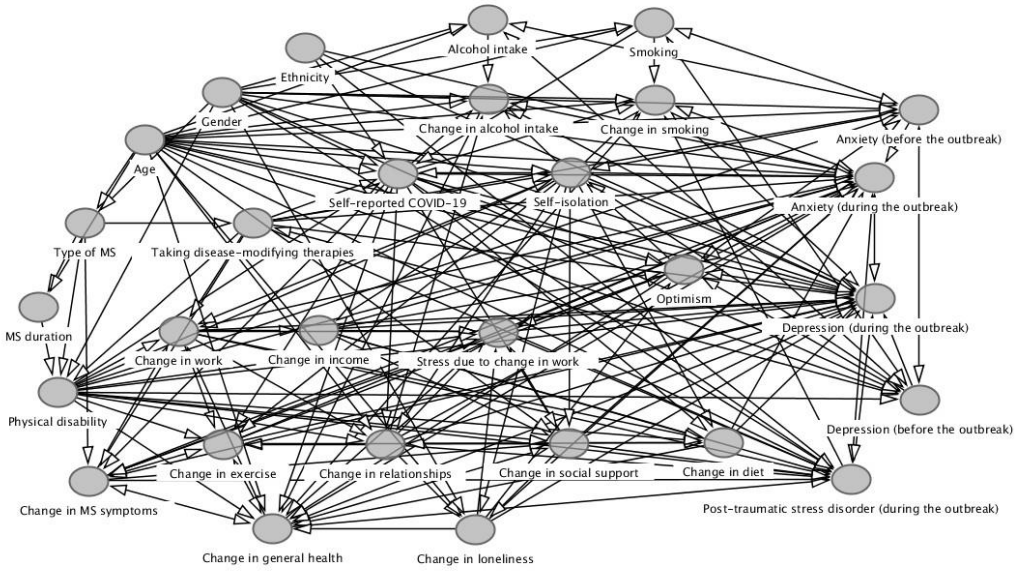

Figure 5-C.1. The parent DAG used for creating regression analyses models for studying the association between different variables within the study's MS population. A separate DAG was used for each exposure and outcome model, by removing different variables, as the total effect of an exposure on an outcome could not be estimated at times due to the complex interrelations of variables.

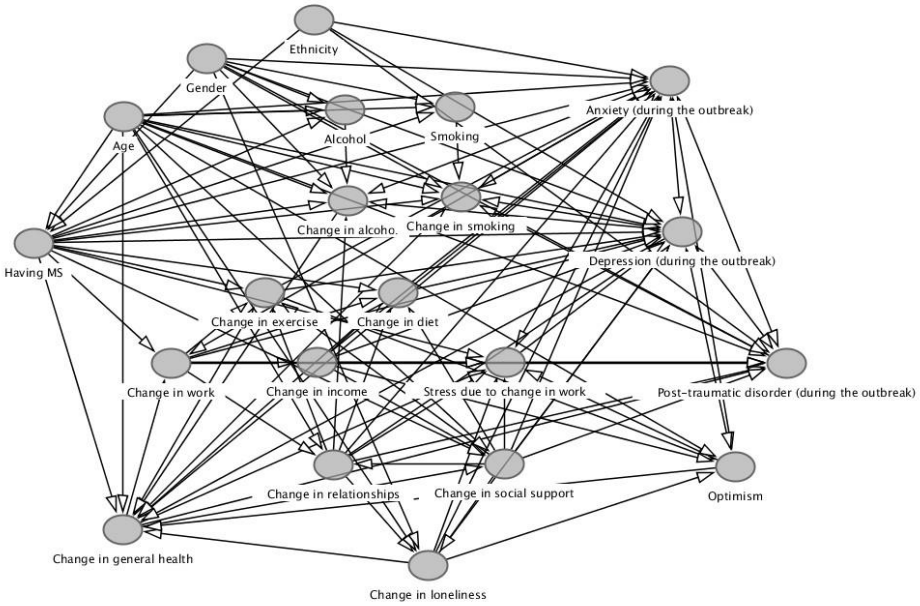

Figure 5-C.2. DAG for creating regression analyses models to compare variables between people with MS and controls.

The DAGitty code for creating the DAG (at https://dagitty.net/dags.html) for

variables in the study's MS population:

```
dag {
bb="0,0,1,1"
"PTSD during the outbreak" [pos="0.881,0.773"]
"anxiety before the outbreak" [pos="0.660,0.399"]
"anxiety during the outbreak" [pos="0.870,0.295"]
"change in MS symptoms" [pos="0.149,0.864"]
"change in alcohol" [pos="0.620,0.232"]
"change in diet" [pos="0.422,0.366"]
"change in exercise" [pos="0.226,0.363"]
"change in general health" [pos="0.148,0.727"]
"change in income" [pos="0.378,0.505"]
"change in loneliness" [pos="0.410,0.865"]
"change in relationships" [pos="0.307,0.655"]
"change in smoking" [pos="0.718,0.177"]
"change in social support" [pos="0.481,0.704"]
"change in work" [pos="0.211,0.512"]
"depression before the outbreak" [pos="0.666,0.633"]
"depression during the outbreak" [pos="0.878,0.513"]
"duration of MS" [pos="0.049,0.455"]
"having COVID-19" [pos="0.230,0.227"]
"physical disability" [pos="0.121,0.605"]
"self-isolation" [pos="0.412,0.223"]
```

"stress due to change in work" [pos="0.566,0.508"]
"taking DMTs" [pos="0.087,0.317"]
"type of MS" [pos="0.055,0.191"]
age [pos="0.085,0.058"]
alcohol [pos="0.615,0.097"]
ethnicity [pos="0.287,0.057"]
gender [pos="0.182,0.088"]
optimism [pos="0.682,0.855"]
smoking [pos="0.714,0.049"]
"PTSD during the outbreak" -> "change in smoking"
"PTSD during the outbreak" <-> "anxiety during the outbreak"
"PTSD during the outbreak" <-> "depression during the outbreak"
"anxiety before the outbreak" -> "anxiety during the outbreak"
"anxiety before the outbreak" -> "self-isolation"
"anxiety before the outbreak" <-> "depression before the outbreak"
"anxiety before the outbreak" <-> alcohol
"anxiety before the outbreak" <-> optimism
"anxiety before the outbreak" <-> smoking
"anxiety during the outbreak" -> "change in MS symptoms"
"anxiety during the outbreak" -> "change in general health"
"anxiety during the outbreak" <-> "change in alcohol"
"anxiety during the outbreak" <-> "change in smoking"
"anxiety during the outbreak" <-> "change in work"
"anxiety during the outbreak" <-> "depression during the outbreak"
"anxiety during the outbreak" <-> "stress due to change in work"
"anxiety during the outbreak" <-> optimism
"change in MS symptoms" -> "PTSD during the outbreak"
"change in MS symptoms" -> "change in social support"
"change in MS symptoms" -> "change in work"
"change in MS symptoms" -> "stress due to change in work"
"change in MS symptoms" <-> "change in exercise"
"change in MS symptoms" <-> "change in general health"
"change in alcohol" -> "change in general health"
"change in alcohol" <-> "depression during the outbreak"
"change in diet" -> "anxiety during the outbreak"
"change in diet" -> "change in general health"
"change in diet" -> "depression during the outbreak"
"change in exercise" -> "anxiety during the outbreak"
"change in exercise" -> "depression during the outbreak"
"change in exercise" -> optimism
"change in exercise" <-> "change in general health"
"change in general health" -> "PTSD during the outbreak"
"change in general health" -> "change in social support"
"change in general health" -> "change in work"
"change in general health" -> "stress due to change in work"
"change in general health" <-> "change in smoking"
"change in income" -> "PTSD during the outbreak"

"change in income" -> "anxiety during the outbreak"
"change in income" -> "change in diet"
"change in income" -> "change in social support"
"change in income" -> "depression during the outbreak"
"change in income" -> "stress due to change in work"
"change in income" -> optimism
"change in loneliness" -> "anxiety during the outbreak"
"change in loneliness" -> "change in general health"
"change in loneliness" -> "depression during the outbreak"
"change in loneliness" -> "stress due to change in work"
"change in loneliness" -> optimism
"change in relationships" -> "PTSD during the outbreak"
"change in relationships" -> "anxiety during the outbreak"
"change in relationships" -> "change in alcohol"
"change in relationships" -> "change in diet"
"change in relationships" -> "change in exercise"
"change in relationships" -> "change in loneliness"
"change in relationships" -> "depression during the outbreak"
"change in relationships" -> "stress due to change in work"
"change in smoking" <-> "depression during the outbreak"
"change in social support" -> "PTSD during the outbreak"
"change in social support" -> "anxiety during the outbreak"
"change in social support" -> "change in diet"
"change in social support" -> "change in exercise"
"change in social support" -> "change in loneliness"
"change in social support" -> "change in relationships"
"change in social support" -> "depression during the outbreak"
"change in social support" -> "stress due to change in work"
"change in work" -> "PTSD during the outbreak"
"change in work" -> "change in diet"
"change in work" -> "change in exercise"
"change in work" -> "change in income"
"change in work" -> "change in relationships"
"change in work" -> "depression during the outbreak"
"change in work" -> "stress due to change in work"
"depression before the outbreak" -> "depression during the outbreak"
"depression before the outbreak" -> "self-isolation"
"depression before the outbreak" <-> "taking DMTs"
"depression before the outbreak" <-> alcohol
"depression before the outbreak" <-> optimism
"depression before the outbreak" <-> smoking
"depression during the outbreak" -> "change in MS symptoms"
"depression during the outbreak" -> "change in general health"
"depression during the outbreak" <-> optimism
"duration of MS" -> "physical disability"
"having COVID-19" -> "PTSD during the outbreak"
"having COVID-19" -> "anxiety during the outbreak"

"having COVID-19" -> "change in MS symptoms"
"having COVID-19" -> "change in alcohol"
"having COVID-19" -> "change in diet"
"having COVID-19" -> "change in exercise"
"having COVID-19" -> "change in general health"
"having COVID-19" -> "change in relationships"
"having COVID-19" -> "change in smoking"
"having COVID-19" -> "change in social support"
"having COVID-19" -> "depression during the outbreak"
"having COVID-19" -> optimism
"having COVID-19" <-> "self-isolation"
"physical disability" -> "PTSD during the outbreak"
"physical disability" -> "anxiety before the outbreak"
"physical disability" -> "anxiety during the outbreak"
"physical disability" -> "change in diet"
"physical disability" -> "change in exercise"
"physical disability" -> "change in general health"
"physical disability" -> "change in relationships"
"physical disability" -> "change in social support"
"physical disability" -> "change in work"
"physical disability" -> "depression before the outbreak"
"physical disability" -> "depression during the outbreak"
"physical disability" -> "having COVID-19"
"physical disability" -> "self-isolation"
"physical disability" -> "stress due to change in work"
"self-isolation" -> "anxiety during the outbreak"
"self-isolation" -> "change in alcohol"
"self-isolation" -> "change in diet"
"self-isolation" -> "change in exercise"
"self-isolation" -> "change in income"
"self-isolation" -> "change in loneliness"
"self-isolation" -> "change in relationships"
"self-isolation" -> "change in smoking"
"self-isolation" -> "change in social support"
"self-isolation" -> "change in work"
"self-isolation" -> "depression during the outbreak"
"stress due to change in work" -> "PTSD during the outbreak"
"stress due to change in work" -> "depression during the outbreak"
"taking DMTs" -> "PTSD during the outbreak"
"taking DMTs" -> "anxiety before the outbreak"
"taking DMTs" -> "anxiety during the outbreak"
"taking DMTs" -> "change in MS symptoms"
"taking DMTs" -> "change in work"
"taking DMTs" -> "depression during the outbreak"
"taking DMTs" -> "having COVID-19"
"taking DMTs" -> "physical disability"
"taking DMTs" -> "self-isolation"

"type of MS" -> "change in MS symptoms"
"type of MS" -> "duration of MS"
"type of MS" -> "physical disability"
"type of MS" -> "taking DMTs"
age -> "PTSD during the outbreak"
age -> "anxiety before the outbreak"
age -> "anxiety during the outbreak"
age -> "change in alcohol"
age -> "change in general health"
age -> "change in loneliness"
age -> "change in relationships"
age -> "change in smoking"
age -> "change in social support"
age -> "depression before the outbreak"
age -> "depression during the outbreak"
age -> "duration of MS"
age -> "having COVID-19"
age -> "self-isolation"
age -> "type of MS"
age -> alcohol
age -> optimism
age -> smoking
alcohol -> "change in alcohol"
ethnicity -> "PTSD during the outbreak"
ethnicity -> "anxiety during the outbreak"
ethnicity -> "depression during the outbreak"
ethnicity -> "having COVID-19"
gender -> "PTSD during the outbreak"
gender -> "anxiety before the outbreak"
gender -> "anxiety during the outbreak"
gender -> "change in alcohol"
gender -> "change in loneliness"
gender -> "change in smoking"
gender -> "depression before the outbreak"
gender -> "depression during the outbreak"
gender -> "having COVID-19"
gender -> "physical disability"
gender -> "type of MS"
gender -> alcohol
gender -> smoking
optimism -> "change in MS symptoms"
optimism -> "change in general health"
optimism -> "self-isolation"
optimism -> "stress due to change in work"
smoking -> "change in smoking"
smoking -> "having COVID-19"
}

The DAGitty code for creating the DAG (at https://dagitty.net/dags.html) for comparison of variables between people with MS and controls:

```
dag {
bb="0,0,1,1"
"PTSD during the outbreak" [pos="0.881,0.773"]
"anxiety during the outbreak" [pos="0.870,0.295"]
"change in alcohol" [pos="0.620,0.232"]
"change in diet" [pos="0.422,0.366"]
"change in exercise" [pos="0.226,0.363"]
"change in general health" [pos="0.148,0.727"]
"change in income" [pos="0.378,0.505"]
"change in loneliness" [pos="0.410,0.865"]
"change in relationships" [pos="0.307,0.655"]
"change in smoking" [pos="0.718,0.177"]
"change in social support" [pos="0.481,0.704"]
"change in work" [pos="0.211,0.512"]
"depression during the outbreak" [pos="0.878,0.513"]
"having MS" [pos="0.057,0.285"]
"stress due to change in work" [pos="0.625,0.595"]
age [pos="0.085,0.058"]
alcohol [pos="0.615,0.097"]
ethnicity [pos="0.287,0.057"]
gender [pos="0.182,0.088"]
optimism [pos="0.682,0.855"]
smoking [pos="0.714,0.049"]
"PTSD during the outbreak" -> "change in smoking"
"PTSD during the outbreak" <-> "anxiety during the outbreak"
"PTSD during the outbreak" <-> "depression during the outbreak"
"anxiety during the outbreak" -> "change in general health"
"anxiety during the outbreak" <-> "change in alcohol"
"anxiety during the outbreak" <-> "change in smoking"
"anxiety during the outbreak" <-> "change in work"
"anxiety during the outbreak" <-> "depression during the outbreak"
"anxiety during the outbreak" <-> "stress due to change in work"
"anxiety during the outbreak" <-> optimism
"change in alcohol" -> "change in general health"
"change in alcohol" <-> "depression during the outbreak"
"change in diet" -> "anxiety during the outbreak"
"change in diet" -> "change in general health"
"change in diet" -> "depression during the outbreak"
"change in exercise" -> "anxiety during the outbreak"
"change in exercise" -> "depression during the outbreak"
"change in exercise" -> optimism
"change in exercise" <-> "change in general health"
"change in general health" -> "PTSD during the outbreak"
```

"change in general health" -> "change in social support"
"change in general health" -> "change in work"
"change in general health" -> "stress due to change in work"
"change in general health" <-> "change in smoking"
"change in income" -> "PTSD during the outbreak"
"change in income" -> "anxiety during the outbreak"
"change in income" -> "change in diet"
"change in income" -> "change in social support"
"change in income" -> "depression during the outbreak"
"change in income" -> "stress due to change in work"
"change in income" -> optimism
"change in loneliness" -> "anxiety during the outbreak"
"change in loneliness" -> "change in general health"
"change in loneliness" -> "depression during the outbreak"
"change in loneliness" -> "stress due to change in work"
"change in loneliness" -> optimism
"change in relationships" -> "PTSD during the outbreak"
"change in relationships" -> "anxiety during the outbreak"
"change in relationships" -> "change in alcohol"
"change in relationships" -> "change in diet"
"change in relationships" -> "change in exercise"
"change in relationships" -> "change in loneliness"
"change in relationships" -> "depression during the outbreak"
"change in relationships" -> "stress due to change in work"
"change in smoking" <-> "depression during the outbreak"
"change in social support" -> "PTSD during the outbreak"
"change in social support" -> "anxiety during the outbreak"
"change in social support" -> "change in diet"
"change in social support" -> "change in exercise"
"change in social support" -> "change in loneliness"
"change in social support" -> "change in relationships"
"change in social support" -> "depression during the outbreak"
"change in social support" -> "stress due to change in work"
"change in work" -> "PTSD during the outbreak"
"change in work" -> "change in diet"
"change in work" -> "change in exercise"
"change in work" -> "change in income"
"change in work" -> "change in relationships"
"change in work" -> "depression during the outbreak"
"change in work" -> "stress due to change in work"
"depression during the outbreak" -> "change in general health"
"depression during the outbreak" <-> optimism
"having MS" -> "anxiety during the outbreak"
"having MS" -> "change in alcohol"
"having MS" -> "change in diet"
"having MS" -> "change in exercise"
"having MS" -> "change in general health"

"having MS" -> "change in smoking"
"having MS" -> "change in social support"
"having MS" -> "change in work"
"having MS" -> "depression during the outbreak"
"having MS" -> "stress due to change in work"
"having MS" -> alcohol
"having MS" -> smoking
"stress due to change in work" -> "PTSD during the outbreak"
"stress due to change in work" -> "depression during the outbreak"
age -> "PTSD during the outbreak"
age -> "anxiety during the outbreak"
age -> "change in alcohol"
age -> "change in general health"
age -> "change in loneliness"
age -> "change in relationships"
age -> "change in smoking"
age -> "change in social support"
age -> "depression during the outbreak"
age -> "having MS"
age -> alcohol
age -> optimism
age -> smoking
alcohol -> "change in alcohol"
ethnicity -> "PTSD during the outbreak"
ethnicity -> "anxiety during the outbreak"
ethnicity -> "depression during the outbreak"
ethnicity -> "having MS"
gender -> "PTSD during the outbreak"
gender -> "anxiety during the outbreak"
gender -> "change in alcohol"
gender -> "change in loneliness"
gender -> "change in smoking"
gender -> "depression during the outbreak"
gender -> "having MS"
gender -> alcohol
gender -> smoking
optimism -> "change in general health"
optimism -> "stress due to change in work"
smoking -> "change in smoking"
}

Appendix 7-A

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Impact of mass vaccination on SARS-CoV-2 infections among multiple sclerosis patients taking immunomodulatory disease-modifying therapies in England

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ABSTRACT

Background: Contradicting assumptions have been made about the effectiveness of SARS-CoV-2 vaccines in patients with multiple sclerosis (MS) receiving immunomodulatory disease-modifying therapies (DMTs) based on the quantification of humoral and cellular immune responses. This study aimed to understand changes in the risk of SARS-CoV-2 infection among the total population of patients receiving MS DMTs in England following mass vaccination.

Methods: This is a retrospective analysis of national data collected prospectively and longitudinally. National Health Service (NHS) England and NHS Improvement (NHSE/I) hold prescribing data on all commissioned MS DMTs in England. United Kingdom Health Security Agency (UKHSA) has been collecting data on all registered SARS-CoV-2 test results, including polymerase chain reaction and rapid antigen tests. All patients receiving MS DMTs were identified using NHSE/I datasets. All patients receiving MS DMTs with SARS-CoV-2 infection (i.e., positive test) from March 2020 to August 2021 were identified by merging NHSE/I and UKHSA datasets. Similar data for the general population were captured using publicly available datasets of the United Kingdom government. The incidence rate ratios (IRR) of SARS-CoV-2 infection among patients receiving MS DMTs compared to the general population during the pre-vaccination (November 2020 to January 2021) and post-vaccination (June to August 2021) periods were calculated.

Results: A mean (standard deviation) of 41,208 (4,301) patients received an MS DMT in England during each month from March 2020 to August 2021. The IRR (95% confidence interval) of infection in patients taking ocrelizumab versus the general population increased from 1.13 (0.97–1.31) during the pre-vaccination period to 1.79 (1.57–2.03) during the post-vaccination period. For patients on fingolimod, it increased from 0.87 (0.73–1.02) to 1.40 (1.20–1.63) during the same periods. There were no significant changes for patients on other MS DMTs.

Conclusion: SARS-CoV-2 vaccines offer less protection against infection to patients taking ocrelizumab or fingolimod, who have an impaired immune response to vaccines, than the general population. These findings will have implications for vaccination policies.

1. Introduction

While real-world data in the general population continue to show that SARS-CoV-2 vaccination is effective in preventing infections (Pritchard et al., 2021), it is still unclear whether it offers the same level of protection to multiple sclerosis (MS) patients receiving

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immunomodulatory disease-modifying therapies (DMTs). Immunological studies are reporting on humoral and cellular immune responses to SARS-CoV-2 vaccines among patients on MS DMTs (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Gadani et al., 2021; Sormani et al., 2021), but they lack findings on the effectiveness of vaccines in preventing infections in this population. It is important that monitoring the population effect of SARS-CoV-2 vaccination is inclusive of patients on immunomodulatory treatments (Pritchard et al., 2021), especially as COVID-19 restrictions are being relaxed.

The present study aimed to understand the impact of mass SARS-CoV-2 vaccination in preventing SARS-CoV-2 (symptomatic and asymptomatic) infections on the entire population of patients taking MS DMTs in England.

2. Materials and methods

This is a retrospective analysis of prospectively and longitudinally collected national data by the National Health Service (NHS) England and NHS Improvement (NHSE/I) and the United Kingdom Health Security Agency (UKHSA).

2.1. Population data

NHSE/I acquire prescribing data on all commissioned MS DMTs in England (National Health Service England, 2018 2021). The total number of patients on MS DMTs (including alemtuzumab, beta-interferons, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, and teriflunomide) during each month from March 2020 to August 2021 was estimated based on their last DMT prescription any time before and including the last day of each month since January 2019.

The total population of England was captured from publicly available data (Office for National Statistics, 2021). The population of adults aged 20 years or above was used to match the MS population who over 98% of them are adults (The Multiple Sclerosis International Federation, 2020).

2.2. SARS-CoV-2 infection data

UKHSA has collected data on all registered SARS-CoV-2 test results, including polymerase chain reaction (PCR) and rapid antigen tests (RAT), from the start of the pandemic which is publicly available for the general population (United Kingdom Government, 2021). The datasets of NHSE/I and UKHSA were merged to identify all patients taking MS DMTs who tested positive for SARS-CoV-2 during each month from March 2020 to August 2021. The last prescribed MS DMT any time before the date of a positive test was used to determine the DMT an MS patient was taking when they tested positive.

The available data on SARS-CoV-2 infections for both MS patients and the general population included people with 1) positive PCR, 2) positive RAT confirmed by positive PCR taken within 72 h, or 3) positive RAT when PCR was not done within 72 h (89.8%, 7.4%, and 2.8% of cases in the general population by the end of August 2021, respectively) (United Kingdom Government, 2021). People with positive RAT but negative PCR within 72 h were not included as a case of SARS-CoV-2 infection. People with more than one positive test were counted once and the date of their first positive test was used.

2.3. Statistical analysis

The incidence rate of SARS-CoV-2 infection was calculated for the general population and patients on MS DMTs. The incidence rate ratio (IRR) was calculated as the incidence rate of SARS-CoV-2 infection among patients taking MS DMTs divided by the incidence rate among the general population. The 95% confidence interval (CI) was estimated using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

In England, mass SARS-CoV-2 vaccination started in December 2020 and COVID-19 restrictions were gradually lifted from March to July 2021. The IRR and 95% CI were calculated for each month during the study period as well as during two waves of the COVID-19 pandemic: (1) three months around the start time of mass SARS-CoV-2 vaccination (November 2020 to January 2021) referred to as *pre-vaccination*, and (2) three months after the start of mass vaccination (June to August 2021) referred to as *post-vaccination*.

3. RESULTS

A mean (standard deviation) of 41,208 (4301) MS patients received DMTs in England during each month from March 2020 to August 2021. A total of 3524 patients taking MS DMTs had SARS-CoV-2 infection during this period.

The monthly incidence rate of SARS-CoV-2 infection among patients on MS DMTs and the general population is presented in Fig. 1 and Supplementary Material 1. The IRR (95% CI) of infection for patients on ocrelizumab versus the general population significantly increased from 1.13 (0.97–1.31), pre-vaccination, to 1.79 (1.57–2.03), post-vaccination (Fig. 2). For patients on fingolimod, this also significantly increased from 0.87 (0.73–1.02) to 1.40 (1.20–1.63) (Fig. 2). There were no significant changes for patients on other MS DMTs (Supplementary Material 2 and 3).

4. Discussion

This study presents the incidence of SARS-CoV-2 infection for the entire population of MS patients receiving DMTs in England and compares their risk of infection to the general population before implementation of mass SARS-CoV-2 vaccination and when at least 74% and 56% of the adult population had received their first and second doses of vaccine, respectively (United Kingdom Government, 2021). To our knowledge, this is the first study to report changes in the risk of SARS-CoV-2 infection in relation to mass vaccination in a population under immunomodulatory therapies. Although individual-level data on SARS-CoV-2 vaccination was not available at the time of the study, the MS population were expected to have a similar pattern of vaccination to the general population as they had a high willingness to be vaccinated (Huang et al., 2021), or may have been vaccinated earlier (patients with severe neurological disabilities or those taking alemtuzumab or ocrelizumab) (UK Health Security Agency, 2020). The study used positive SARS-CoV-2 test results which includes both symptomatic and asymptomatic infections.

The findings of this study show a substantial increase in the risk of SARS-CoV-2 infection among patients on ocrelizumab or fingolimod compared to the general population following the liberalization of COVID-19 restrictions and despite mass vaccination. There were no obvious changes in the risk of infection among patients taking other MS DMTs.

Patients on ocrelizumab and rituximab show reduced antibody and memory B-cell responses to SARS-CoV-2 vaccines (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Gadani et al., 2021; Sormani et al., 2021). Nevertheless, they can mount a T-cell response to these vaccines (Apostolidis et al., 2021; Brill et al., 2021; Gadani et al., 2021). It is unknown how this interplay between humoral and cellular immune responses translate into protecting patients on these anti-CD20 B-cell depleting therapies from infection. Fingolimod also seems to prevent the production of antibodies in response to SARS-CoV-2 vaccination (Achiron et al., 2021; Sormani et al., 2021). So far, assumptions about the impact of MS DMTs on the effectiveness of SARS-CoV-2 vaccines are based on experiences with previous vaccinations and these immunological studies rather than population-based studies (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Cabreira et al., 2021; Sormani et al., 2021). Cohort studies to assess the effectiveness of

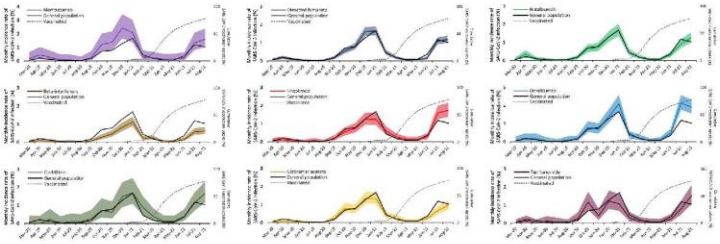

Fig. 1. Monthly incidence rate of SARS-CoV-2 infection among multiple sclerosis (MS) patients receiving disease-modifying therapies (DMTs) versus the general population of 20-years-old or above in England. Data for individual DMTs are presented in separate graphs. The coloured line in each graph is the incidence rate of infection during each month per 100 MS patients taking each DMT, and the shaded areas are the 95% confidence intervals. The black line is the incidence rate of infection during each month per 100 people aged 20 years or above in the general population. The dashed gray line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

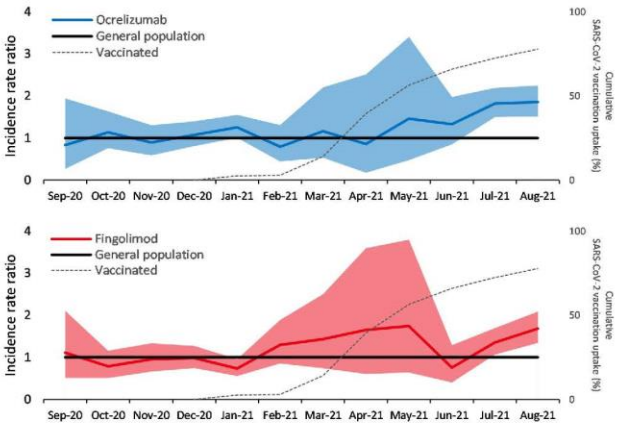

Fig. 2. Incidence rate ratio of SARS-CoV-2 infection among multiple sclerosis (MS) patients taking ocrelizumab and fingolimod compared to the general population aged 20 years or above in England. Data for ocrelizumab (top) and fingolimod (bottom) are presented in separate graphs. The coloured line in each graph is the incidence rate ratio and the shaded area is the 95% confidence interval. The black line demarcates the incidence rate ratio in the general population which is always one and serves as a reference line. The dashed gray line is the cumulative SARS-CoV-2 vaccination (both doses) uptake during each month among the adult population in England.

SARS-CoV-2 vaccines in patients taking MS DMTs have been set up, but it will be a while before they are concluded (Sormani et al., 2021). The findings of our study suggest that the humoral immune response to vaccines, which is suppressed by ocrelizumab and fingolimod and preserved by other MS DMTs (Achiron et al., 2021; Apostolidis et al., 2021; Brill et al., 2021; Sormani et al., 2021), may be mainly responsible for the protection provided against SARS-CoV-2 infection.

We also noted that the risk of SARS-CoV-2 infection associated with beta-interferons was lower than the general population, both pre- and post-vaccination, which is not unexpected given their antiviral effects (Dumitrescu et al., 2021).

The effectiveness of SARS-CoV-2 vaccination in preventing symptomatic infections and severe disease among patients taking MS DMT is yet to be determined. The timing of vaccination in relation to administration of some MS DMTs, such as alemtuzumab, cladribine, and ocrelizumab, can affect the development of an immune response to vaccines (Cabreira et al., 2021) which was not applied in the present study because of individual-level data not being available at the time of this study. Also, other potential confounders, such as age, sex, or place of residence, could not be considered in the analysis because of the same reason.

5. Conclusions

These preliminary findings suggest that SARS-CoV-2 vaccines offer minimal protection against infection to patients taking ocrelizumab or fingolimod. Population studies using individual-level data on vaccination (including interval between vaccination and SARS-CoV-2 infection), antibody levels, infections, and disease severity are required to establish the benefits of current vaccination programmes and offering third dose vaccines to patients with drug-induced immunosuppression.

CRediT authorship contribution statement

Afagh Garjani: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sameer Patel:** Data curation, Investigation, Methodology, Resources, Validation, Writing –

review & editing. **Dhiren Bharkhada:** Conceptualization, Investigation, Methodology, Project administration, Resources, Validation, Writing – review & editing. **Waqar Rashid:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Alasdair Coles:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Graham R Law:** Formal analysis, Methodology, Visualization, Writing – review & editing. **Nikos Evangelou:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interests

Afagh Garjani has received research support from the United Kingdom Multiple Sclerosis Society, speaker honorarium and travel support from the Multiple Sclerosis Academy, and travel support from Novartis and Merck. Sameer Patel declares no competing interests. Dhiren Bharkhada declares no competing interests. Waqar Rashid declares no competing interests. Alasdair Coles declares no competing interests. Graham R Law declares no competing interests. Nikos Evangelou has served as a member of advisory boards for Biogen, Merck, Novartis, and Roche, received grant income from the United Kingdom Multiple Sclerosis Society, Medical Research Council (MRC), Patient-Centered Outcomes Research Institute (PCORI), and National Institute for Health Research (NIHR).

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Funding

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103458.

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Appendix 7-B

Disclosures

- The institution of Dr Afagh Garjani has received research support from the UK MS Society and Merck.
- She has received personal compensation for serving as a speaker with the MS Academy and Biogen.
- She has received travel support for attending educational meetings from Merck and Novartis.

Effectiveness of COVID-19 vaccines in MS patients receiving disease-modifying therapies

Total Population Study of The National Health Service (NHS) England

Afagh Garjani[1], Sameer Patel[2], Graham R Law[3], Dhiren Bharkhada[4], Waqar Rashid[5], Alasdair Coles[6], Nikos Evangelou[1]

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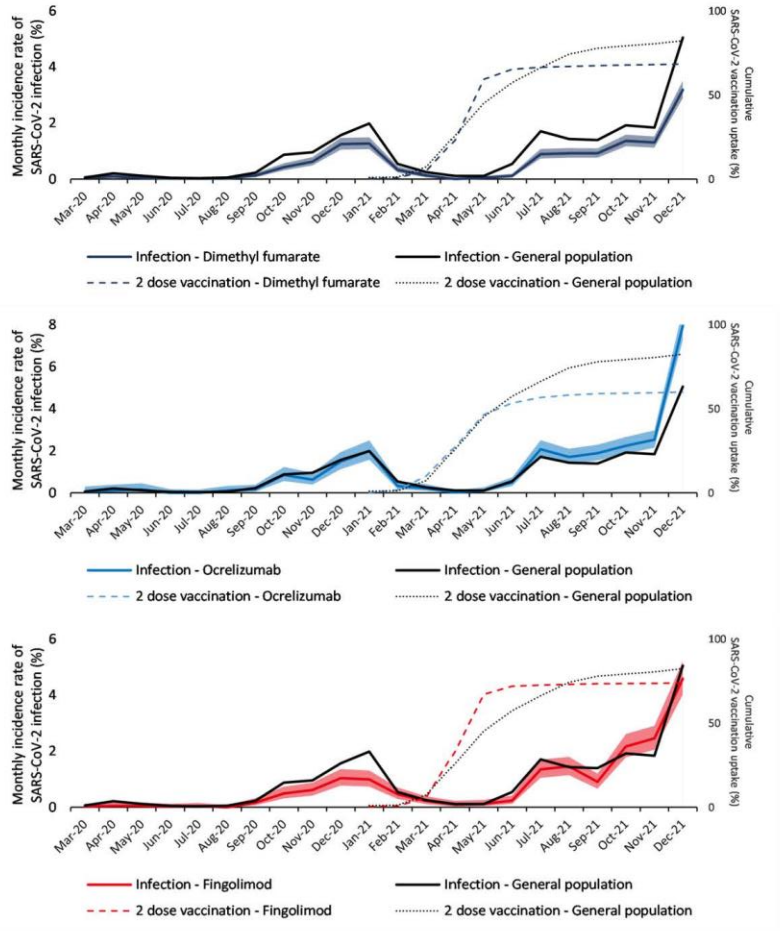
Background

- **The immune response to COVID-19 vaccines varies between different MS DMTs.**
- **COVID-19 vaccines fail to protect MS patients on ocrelizumab or fingolimod from contracting the infection.**



Unpublished data.

AAN 2022 Annual Meeting. S5: COVID and MS Basic Science (S5.008). Impact of Multiple Sclerosis Disease-Modifying Therapies on Effectiveness of SARS-Cov-2 Vaccines

Objective

To assess the occurrence of severe COVID-19 outcomes among vaccinated MS patients on different DMTs

Methods

- **Study design:** prospective and longitudinal cohort
- **Participants:** *all* vaccinated MS patients on a DMT (n =29,353 with two doses)
- **Setting:** England, December 2020-2021
- **Outcomes:** Incidence rate of hospitalisation and in-hospital mortality due to COVID-19

NHS England

UK Health Security Agency

Before the results...

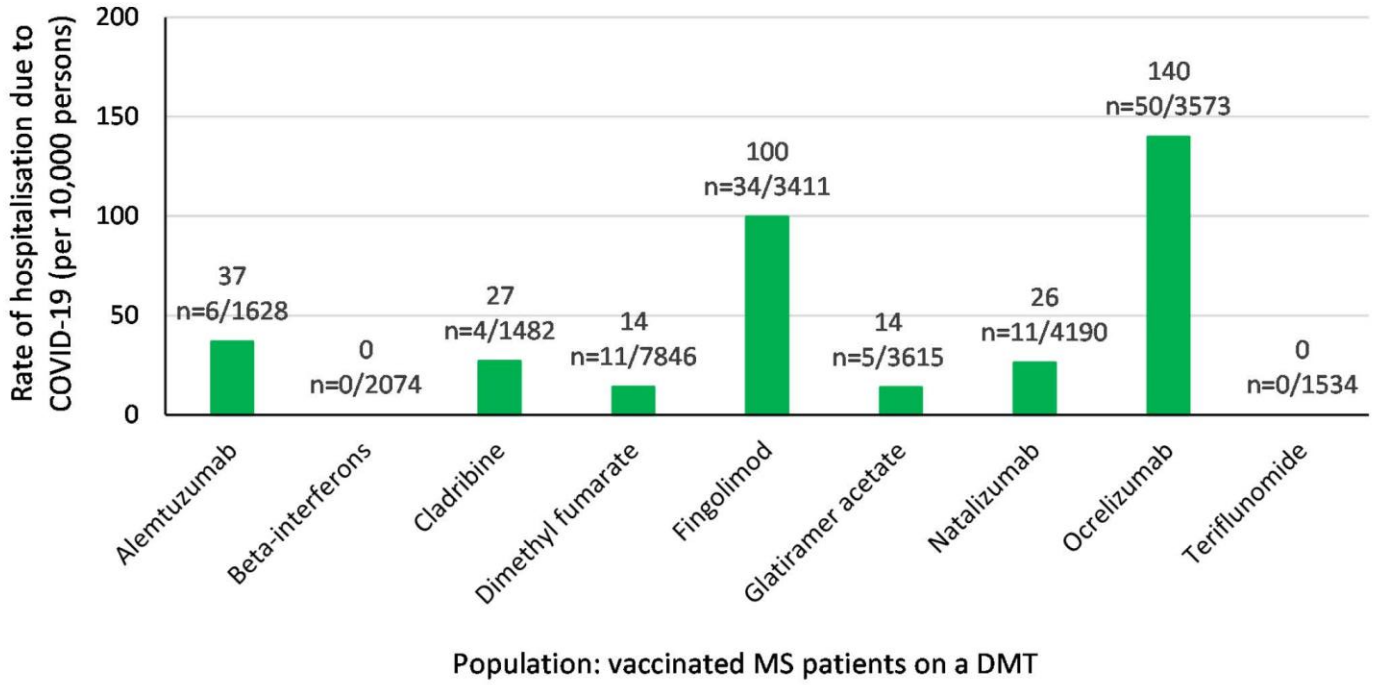
Table 2. Multivariable Multinomial Logistic Regression Model for the Clinical Severity Outcome

Risk factor	COVID-19 clinical course outcome level[a]					
	Hospitalization only, OR (95% CI)	*P* value	ICU and/or required ventilator support, OR (95% CI)	*P* value	Death, OR (95% CI)	*P* value
Disease-modifying therapy						
None	1 [Reference]	NA[b]	1 [Reference]	NA[b]	1 [Reference]	NA[b]
Fumarates	0.99 (0.52-1.88)	.90	0.26 (0.08-0.82)	.98	0.40 (0.09-1.70)	.30
S1PR	0.65 (0.26-1.61)	.23	0.77 (0.28-2.14)	.94	0.86 (0.15-4.93)	.89
Glatiramer acetate	1.15 (0.51-2.61)	.73	NA[b]	.96	0.86 (0.16-4.56)	.89
Interferons	0.35 (0.08-1.57)	.11	0.29 (0.04-2.32)	.98	0.56 (0.06-5.49)	.75
Natalizumab	0.67 (0.31-1.45)	.18	0.09 (0.01-0.73)	.98	0.80 (0.19-3.44)	.96
Ocrelizumab	1.63 (0.98-2.72)	.009	0.91 (0.46-1.80)	.94	0.47 (0.17-1.30)	.25
Other	1.21 (0.45-3.24)	.70	0.50 (0.10-2.38)	.96	0.91 (0.18-4.73)	.83
Rituximab	4.56 (2.10-9.90)	<.001	1.92 (0.61-6.07)	.91	2.81 (0.45-17.70)	.11
Teriflunomide	0.83 (0.34-2.02)	.58	0.30 (0.06-1.37)	.98	0.48 (0.08-3.04)	.57

COVID-19 related hospitalisation rate =19.7% and mortality rate =3.3%

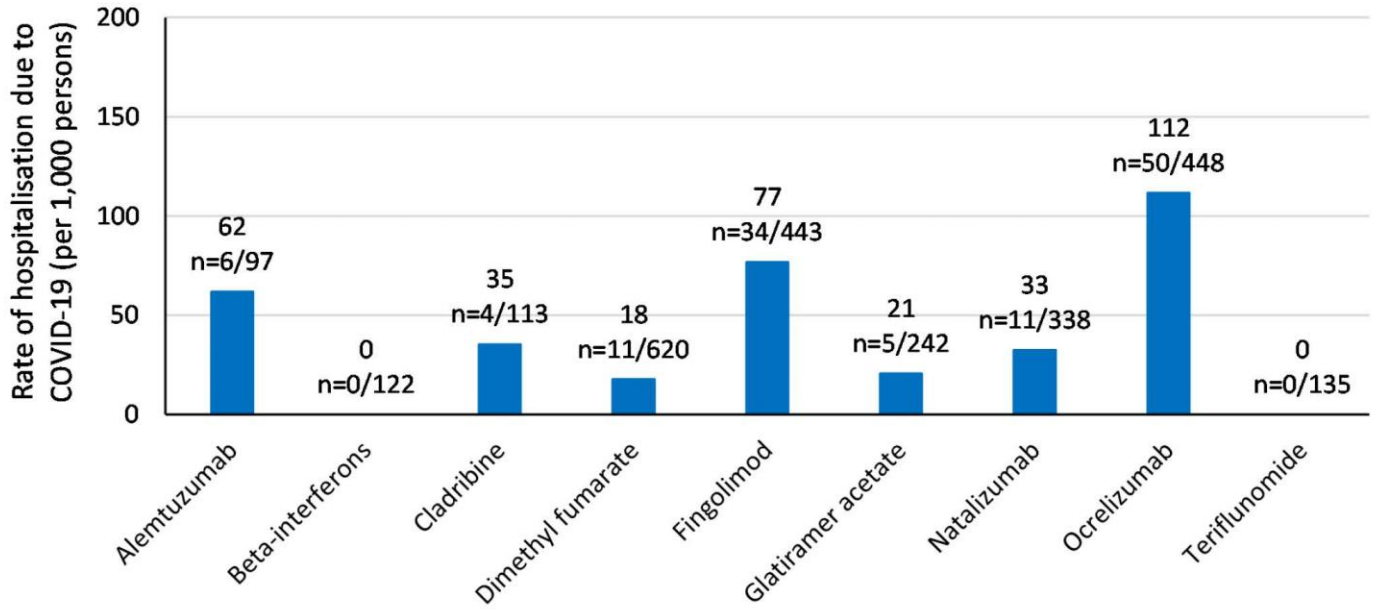
Salter A, et al. Outcomes and risk factors associated with SARS-CoV-2 infection in a North American registry of patients with multiple sclerosis. JAMA neurology. 2021; 78(6): 699-708. doi:10.1001/jamaneurol.2021.0688

Results



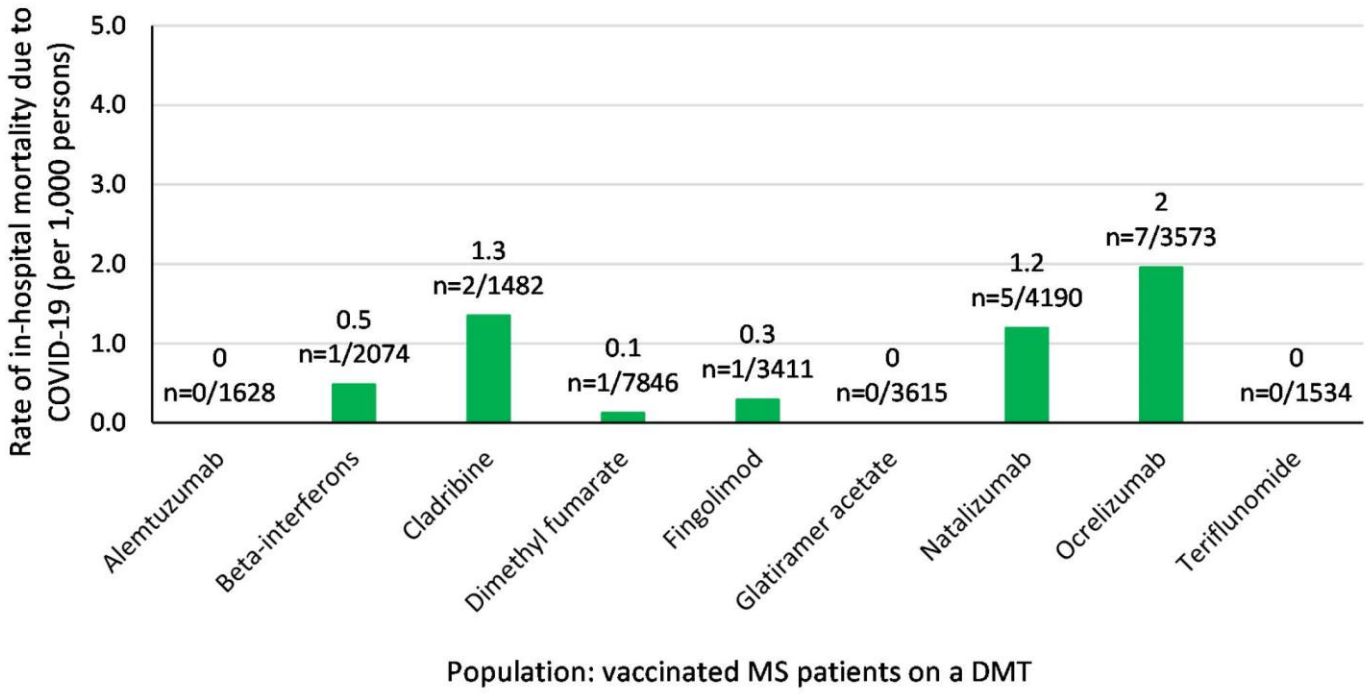
Population: vaccinated MS patients on a DMT

Results

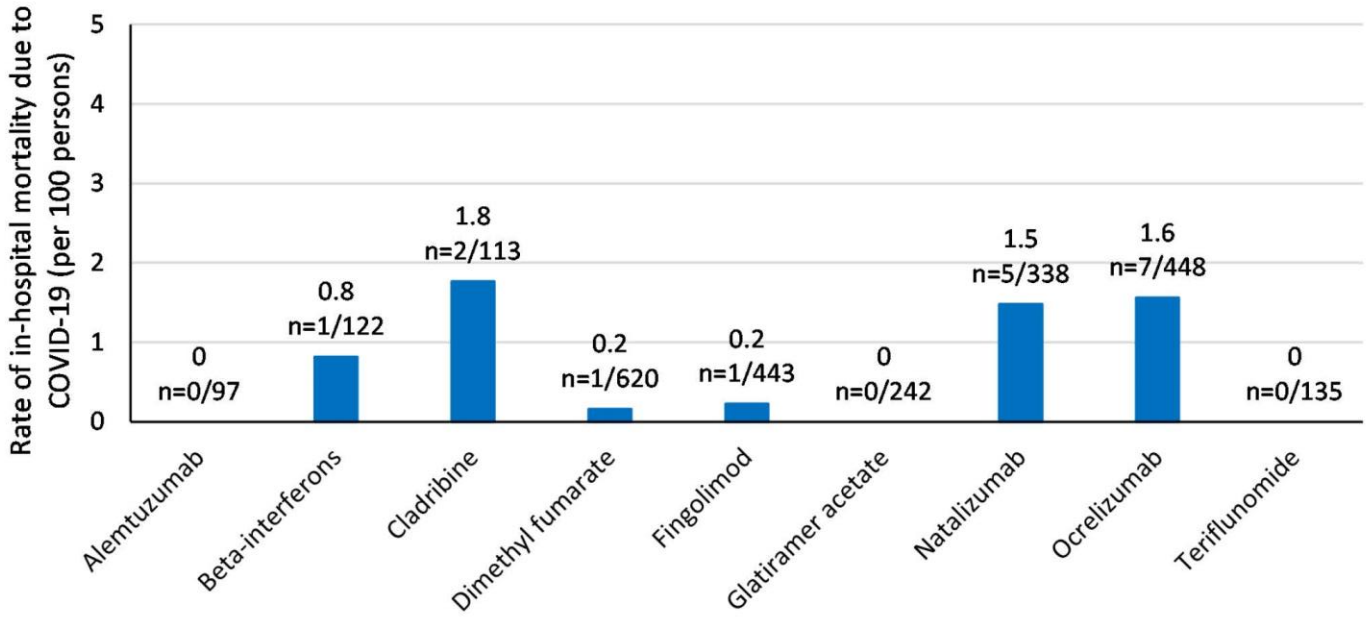


Population: vaccinated MS patients on a DMT with a positive COVID-19 test

Results


Rate of in-hospital mortality due to COVID-19 (per 1,000 persons)
5.0
4.0
3.0
2.0
1.0
0.0
0
n=0/1628
0.5
n=1/2074
1.3
n=2/1482
0.1
n=1/7846
0.3
n=1/3411
0
n=0/3615
1.2
n=5/4190
2
n=7/3573
0
n=0/1534
Alemtuzumab
Beta-interferons
Cladribine
Dimethyl fumarate
Fingolimod
Glatiramer acetate
Natalizumab
Ocrelizumab
Teriflunomide
Population: vaccinated MS patients on a DMT

Results



Population: vaccinated MS patients on a DMT with a positive COVID-19 test

Results

- Following 3rd COVID-19 vaccine, there were no hospitalisations with any of the MS DMTs, except for:
  - Ocrelizumab: 4 out of 65 infections (6%) → no mortality
  - Fingolimod: 11 out of 78 infections (14%) → no mortality

Future analysis

- To determine whether these observations are due to COVID-19 vaccine ineffectiveness, SARS-CoV-2 variants, or treatment approach
- To assess the duration COVID-19 vaccines offer protection
- To assess the role of age, frailty, and socioeconomic status
- To assess the effects of anti-COVID-19 treatments

Conclusion

- Although COVID-19 related hospitalisation rate for vaccinated MS patients on DMTs is lower than early stages of the pandemic, it is still higher for ocrelizumab or fingolimod.
- Although COVID-19 related mortality for vaccinated MS patients on DMTs is lower than early stages of the pandemic, it is still higher for ocrelizumab.

Appendix 8-A

MULTIPLE SCLEROSIS JOURNAL | MSJ

Topical Review

Decentralised clinical trials in multiple sclerosis research

Afagh Garjani, Brandon Jun-Yu Liu, Christopher Martin Allen, Douglas David Gunzler, Stephen William Gerry, Sarah Marie Planchon, Roshan das Nair, Jeremy Chataway, Emma C Tallantyre, Daniel Ontaneda and Nikos Evangelou

Multiple Sclerosis Journal
2023, Vol. 29(3) 317–325
DOI: 10.1177/13524585221100401

Abstract: Randomised controlled trials (RCTs) play an important role in multiple sclerosis (MS) research, ensuring that new interventions are safe and efficacious before their introduction into clinical practice. Trials have been evolving to improve the robustness of their designs and the efficiency of their conduct. Advances in digital and mobile technologies in recent years have facilitated this process and the first RCTs with decentralised elements became possible. Decentralised clinical trials (DCTs) are conducted remotely, enabling participation of a more heterogeneous population who can participate in research activities from different locations and at their convenience. DCTs also rely on digital and mobile technologies which allows for more flexible and frequent assessments. While hospitals quickly adapted to e-health and telehealth assessments during the COVID-19 pandemic, the conduct of conventional RCTs was profoundly disrupted. In this paper, we review the existing evidence and gaps in knowledge in the design and conduct of DCTs in MS.

Keywords: Decentralised, clinical trial, randomised controlled trial, multiple sclerosis, remote, digital

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Introduction

Randomised controlled trials (RCTs) are an essential component of modern healthcare, ensuring that new interventions are safe and efficacious before their introduction into clinical practice. RCTs, however, are expensive, time-consuming and burdensome to participants, investigators and funders, highlighting a need for innovations that reduce their high 'failure' rate.[1–4] Success may be threatened, for example, by lack of funding due to prohibitively high costs,[1,3] low statistical power due to failure to recruit or retain participants[3,5] or lack of generalisability due to being biased towards a certain population (e.g. towards individuals who are more able to attend in-person study visits).[3,6] Therefore, initiatives are being developed to optimise the efficiency of the conduct of RCTs; decentralised clinical trials (DCTs) being one of these innovations.[7–9]

DCTs are defined as trials in which different elements of the trial such as recruitment, delivery and administration of interventions, study visits, assessment of outcomes and data collection are executed remotely.[10,11] They obviate the need to travel to a trial centre for participants, and therefore, enable participation from different locations by people who may not have been able to participate in the trial otherwise.[10,11] DCTs frequently rely on digital and mobile technologies, allowing for more flexible assessments that are not bound by the limitations of scheduled on-site study visits.[10] A transition from conventional, centralised RCTs to DCTs was on the horizon prior to the COVID-19 pandemic,[7,8,10] but the demand for such evolution in the design and conduct of RCTs has been recognised more widely during the pandemic and some of their techniques have been rapidly adopted.[12–14]

RCTs play an important role in multiple sclerosis (MS) research as new disease-modifying therapies (DMTs) and symptomatic treatments are still required. In this paper, we review the existing evidence and gaps in knowledge in designing and conducting DCTs in MS research.

After the parameters and scope of the review were agreed by the authors, PubMed and Google Scholar databases and the Google search engine were searched

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through July 2021 using the keywords (in different combinations) 'decentralised (or decentralized), randomised (or randomized) controlled trial (or clinical trial or trial), remote, digital, virtual, online, and electronic' and 'multiple sclerosis'. For each section, outlined in the review, additional keywords, corresponding to each topic, were used for a more targeted search. All relevant articles and the references cited in these articles were reviewed. If MS-specific articles for any of the sections were considered insufficient, a similar search was performed after excluding the keyword 'multiple sclerosis' to find relevant articles from other fields of neurology or medicine.

Conceptual framework

To ensure that RCTs are appropriately powered for testing the efficacy of a treatment within a limited sample size, they are performed under controlled circumstances where participants tend to have homogeneous characteristics.[15] Therefore, the findings of RCTs are typically not generalisable, and trials of treatments in real-world populations and under usual clinical practice settings are required to test their effectiveness.[15–17] Trial designs are moving towards integrating efficacy and effectiveness studies to save time and cost.[15] DCTs can help reduce this efficacy–effectiveness gap by enabling the conduct of pragmatic trials on a larger number of participants with more heterogeneous demographic and clinical characteristics from different locations and practice settings.[14,15]

RCTs also examine the efficiency of therapeutic interventions, that is, their cost-effectiveness.[18] There are benefits to undertaking such economic analysis as part of RCTs, such as using prospectively collected patient-level data rather than performing retrospective population studies, but there are also limitations,[18,19] which could be overcome through DCTs. Conventional RCTs may fail to take real-world costs of a treatment into account.[18,20] Since extensions of RCTs can be expensive and demanding for both investigators and participants, the follow-up duration of most conventional RCTs are often too short to collect patient-level data on long-term indirect costs of treatment,[18] such as costs of monitoring MS DMTs, switching MS DMTs or disruptions in their use, their side effects, disability progression due to MS, lost productivity, relapses and hospitalisations.[20] Also, the cost-effectiveness of an MS DMT estimated in a centralised RCT of a few centres may not be applicable to other healthcare settings due to their lack of generalisability.[18] Although DCTs cannot eliminate all these problems, they can improve estimations of cost-effectiveness by enabling incorporation of real-world data into RCTs, allowing for long-term follow-up, and increasing the generalisability of their findings.[21] The costs and savings of applying remote and digital techniques in administration and monitoring of interventions should be carefully calculated when assessing the cost-effectiveness of a proposed treatment in a DCT.

Recruitment, retention and study population

MS already imposes a high burden on patients by adversely affecting their health and productivity and demanding that a substantial proportion of their time is dedicated to their clinical care.[22,23] Participating in trials can further disrupt participants' daily routine and they may incur indirect costs, such as arranging a caregiver.[24,25] Difficulties of transport to the study site or having other commitments appear to be the main reasons for declining participation in, or withdrawal from, a study.[26,27] Therefore, RCTs commonly recruit participants at a slower rate than planned or lose participants to follow-up.[5,28,29] Insufficient recruitment and retention can lead to delays in trial completion, additional costs, underpowered and biased results or premature trial termination.[24,28,30,31] The same issues can also lead to the inadvertent exclusion of some people with disabilities, multiple comorbidities, or caring or job responsibilities, or people who live far away from, often urban, study sites[3,32] and reduce the generalisability of the findings.[6]

DCTs can improve participation in studies and retention of participants by allowing them to engage in research activities without the need to travel to a study site and to undertake these activities at their convenience based on their personal and daily schedule.[10,32,33] For example, people who are unable to walk may be excluded from conventional RCTs, and their participation can be facilitated through DCTs. Therefore, DCTs can include a more diverse group of participants, improving the trial's generalisability and reducing bias.[34] For example, MS patients managed in community health services and those managed in specialist MS clinics can be different populations. The findings of a conventional RCT, which tends to recruit participants from MS clinics and hospital settings, may not be generalisable to the broader MS population.[35] DCTs can be leveraged to enrich recruitment by targeting these underrepresented populations in conventional RCTs. Larger study populations may, however, be required because of the heterogeneous study population and increased variability in outcomes,[36,37]

but this may be a reasonable trade-off for improving the external validity of a trial. The growing use of electronic health records will also facilitate confirmation of diagnosis and review of eligibility criteria during recruitment.

There is a risk that people who prefer in-person interactions or are unable to use digital technologies – for example, due to technological illiteracy, physical disabilities, cognitive or visual problems or lack of resources to support the use of such technologies (e.g. high-speed Internet connections), may still be excluded from DCTs.[38,39] Advancements in technologies may enhance the usability of digital tools for certain populations. In some circumstances, willing friends or family members could be trained to assist participants with completion of their trial activities remotely. Trials may need to consider more complex hybrid designs, which provide both remote and on-site options, to ensure that their study population is representative of the real-world patient population.

MS trials of therapeutic interventions rarely require the identification of participants in inpatient settings. However, RCTs of some acute inpatient treatments, for example, management of severe disabling relapses, will inevitably require recruitment of participants within inpatient settings with remote follow-up, hence, adopting a hybrid approach to RCTs. Moreover, trials that involve imaging outcome measures are more likely to require hybrid designs.

Study visits

The growing use of telehealth and e-health tools in routine care of people with MS facilitates the shift towards remote study visits in RCTs.[40,41] For example, these tools are already being used for providing information regarding a study and remote consenting, including real-time interaction between potential participants and the research staff to ensure that an informed decision is made.[42,43] The digitisation of other components of a study visit will be reviewed in the following sections.

Outcome measures

Clinical

The prospect of digitising outcome measures has played a role in envisaging a future where DCTs are practical.[44] We report on how digital technologies can reshape RCTs but the specifics of each digitised outcome measure are beyond the scope of this review.

Several existing outcome measures are being or have been converted into tele- or digital assessments to enable remote monitoring of participants and providing them with flexibility in timing their research activities (e.g. the Expanded Disability Status Scale or the Multiple Sclerosis Functional Composite).[39,44,45] This approach allows for more frequent and even continuous assessments (as opposed to infrequent in-person study visits that tend to be restricted by time), leading to increased power of a study.

People with MS commonly experience fluctuations in their physical and cognitive performance, sometimes exacerbated by the fatigue associated with travel to study sites, which can affect the findings of a trial depending on participants' performance capacity at the time of testing.[38,46] Repeated measurements can, therefore, be more realistic and closer to participants' natural performance compared to cross-sectional assessments.[38,46] Monitoring composite outcomes in real-time allows for a more dynamic analysis that accounts for the potential relationship between different health-related outcomes,[47] for example, the effects of participants' fatigue, pain or mood on their mobility. Real-time recording of patient-reported outcomes not only prevents recall bias, which is likely to occur with retrospective reporting during study visits, but also enables the integration of subjective perceptions of symptoms and objective measurements (e.g. detecting fever during a presumed MS relapse).[48] E-health and telehealth technologies can improve reporting MS relapses or adverse events in a DCT. The ease and frequency of evaluations in a DCT may, however, lead to over-reporting of side effects compared to conventional RCTs.[44]

Furthermore, the emerging digital evolution in the provision of healthcare presents an opportunity to use routinely collected clinical data in DCTs.[44] Linking electronic health records to electronic records of RCTs will enable the use of real-world data and outcomes, such as hospital admissions and potential adverse events, which might, otherwise, go unreported.[49]

The digital era has also unlocked opportunities to develop new outcome measures or to assess additional aspects of participants' performance when using existing ones.[38,39] Portable and wearable devices, such as smartphones and smartwatches, enable measurement of participants' physical activity through both passive monitoring and active instructed tests,[28,39,48] and their use appears to be acceptable to people with MS.[28] These technologies not only capture conventional measures of physical disability in MS, such as

mobility or dexterity, but also introduce objective measurements of other aspects of physical health, such as falls, fatigue, sleep and autonomic dysfunction, which commonly affect the quality of life of people with MS but can be invisible or difficult to capture in conventional RCTs.[39,48] The application of wearable sensors, however, goes beyond the quantification of physical and physiological features and is also being considered for measuring biomarkers in bodily fluids.[50] Digital tools also allow the assessment of participants' learning curves during repeated tests (e.g. Trail Making Tests A and B, Ishihara test, n-back task and 9-Hole Peg test) to evaluate their ability to learn a task and their response speed in addition to response accuracy.[38]

Digital tools and their remote application will require standardisation and validation before their introduction into RCTs,[13,51] which is being addressed by a growing number of MS-specific studies in recent years.[39,48] Although the outlook for using digital outcome measures is promising, they can still overburden participants with excessive and complex tasks.[32] Research staff often directly oversee the completion of outcome measures during in-person study visits, which improves compliance. While data collection could be negatively affected due to poor compliance of participants when they are asked to report outcome measures remotely, routine checks for compliance (e.g. automated emails that go out if an outcome measure is not completed, followed by personnel contact at the next level) can be built into the structure of DCTs to prevent it. Research staff may need to spend more time following up on missing or invalid data with remote compared to on-site data collection. So, it remains possible that the convenience of DCTs will be offset by the inconvenience of the process of remote data validation.

Imaging

Magnetic resonance imaging (MRI) is one of the most widely used tools in RCTs of MS DMTs.[51] The use of MRI in a trial may limit decentralisation as participants need to travel to a study site to undergo scans. Mobile and community-based MRI scanners are available,[52] and can improve participants' access. Developing and implementing standardised MRI protocols across sites, enabling participants to be scanned at the closest centre, is a practical solution.[53] The use of standardised MRI protocols for MS diagnosis and follow-up is being advanced by international MS associations.[53] They are developing strategies to overcome its challenges, such as scanner differences or engagement of different MRI centres, which can also be employed in MS research.

Therapeutic interventions

Currently, most RCTs of therapeutic interventions in MS that are conducted remotely involve rehabilitation or psychotherapy.[39] To the best of our knowledge, there are no entirely remote RCTs of pharmacological interventions in MS; our search within clinical trial registries (clinicaltrials.gov and the ISRCTN registry) did not reveal any such studies. Although the remote administration and monitoring of rehabilitation or psychotherapy is facilitated through readily available e-health or telehealth technologies, which are currently being used,[39,40,54] this is not yet applicable to pharmacological interventions such as DMTs. Pharmacies are increasingly providing drug delivery services to patients' homes,[55] but the delivery and administration of some investigational medicinal products can be difficult to undertake entirely remotely; they may require specialised handling during delivery (e.g. cold chain management) or close monitoring during administration.[10]

The administration of some treatments, such as drug infusions, must be monitored by healthcare providers, but could be conducted in home settings. Some local healthcare providers already offer these services to people with MS and can be utilised in DCTs involving altered administration of established DMTs (e.g. extended interval dosing of natalizumab).[56] Home visits are an alternative approach (e.g. cardiac monitoring at fingolimod initiation or home administration of steroids for relapses);[57,58] however, the application of these methods to improve participants' access to trials of investigational medicinal products will require the establishment of dedicated local or mobile research centres.

Digital technologies can be employed for remote monitoring of medication usage and measuring adherence. Direct monitoring of participants' adherence to a medication by the research staff can be laborious and expensive, and reporting of drug usage by participants can be unreliable.[59] Digital tools, such as electronic needle disposal systems, electronic pill bottles or electronic diaries enable objective and real-time monitoring of medication usage,[39] which along with electronic drug reminders can improve adherence.[39,59]

Data protection

It is evident that the General Data Protection Regulation and other data privacy regulations will

also apply to DCTs, but additional considerations regarding data safety and security during their collection, transfer, handling, use and storage will be required for these trials.[10,60] While the specifics of these regulations are beyond the scope of this review, some examples include policies for using passive data, linking multiple sources of data and ensuring data security on mobile technologies as well as during their transfer in the complicated process of data flow in DCTs.[60,61]

Although digital technologies, through strategies discussed above, present an opportunity to reduce missing data in an RCT, clear instructions on data management need to be included in study protocols to avoid data loss.[10,60]

Ethics

Institutional Review Boards (IRBs) may be unfamiliar with some approaches that are used in DCTs and have not been widely implemented in trials. As a result, the ethical and regulatory review process for a DCT may be prolonged compared to a conventional RCT. Regulatory bodies and researchers need to work closely with IRBs to ensure that DCTs meet all the criteria for ethical research.

Study sites and setup

It is likely that as centralised RCTs evolve into DCTs, the organisation of study sites will transform as well. Local clinical trial hubs and mobile facilities run by a network of clinical research employees could still perform research activities that cannot currently be done remotely (e.g. MRI scans, sample collections and drug administration). Remote conduct of RCTs can facilitate more widespread involvement of smaller study sites in trials.[13]

Remote study site initiation and staff training has commonly been used during the COVID-19 pandemic, and might be preferred, because it saves time and cost.[62] It is important to ensure that the research staff are trained appropriately for their roles in a DCT, which will entail different responsibilities compared to a conventional RCT (e.g. management of electronic, instead of manual data entries or training participants to use digital tools).[13]

Digital tools should be made user-friendly and run efficiently so that the research staff are not overburdened by tackling technical problems.[32] Implementing a technical core or help centre into the structure of DCTs may alleviate the pressure on research staff.

Costs

RCTs are expensive and digitising them is thought to reduce their cost.[63] A 2011 study showed that decentralised trials have higher data management costs than centralised trials.[64] Although reduced in-person study visits in DCTs will save costs, the added costs of the remote approaches discussed above are study specific. It is likely that advancements in digital technologies (e.g. unified rather than local data storage) and their more widespread use will reduce these costs. Also, the reduced risk of delays in trial completion or its failure is probably an economic advantage of DCTs over conventional RCTs. The evidence regarding the costs of DCTs compared to conventional RCTs is limited, however, and may change over time with developments in DCT designs and their widespread application.

Implementation

The aim of implementation research is to narrow the gap between finding an efficacious and effective intervention and its evidence-based use in clinical practice.[65] Implementation strategies are increasingly being explored within trials to accelerate this process.[65] DCTs will involve remote and potentially novel modes of administering and monitoring treatments that might have not been introduced into routine care. DCTs could demonstrate the feasibility of certain remote processes that could be adopted to introduce efficiencies in clinical practice. Considering implementation issues at early stages of a DCT is vital to ensure that the intervention can be delivered in clinical practice and to identify adaptations required to achieve the same level of effectiveness.

Conclusion

Clinical trial designs continue to evolve with the aim of improving efficiency and robustness. Advancements in digital and mobile technologies in recent years have facilitated this process and initiated what we think is a gradual transformation from centralised to decentralised RCTs. DCTs have the potential to increase the statistical power of RCTs, produce more generalisable and less biased results and run more efficiently compared to conventional RCTs by recruiting large heterogeneous study samples, more frequent assessments of outcome measures, capturing participants' real-world performance and timely trial completion. Organisations have started projects to develop and improve the design and conduct of DCTs.[7–10]

DCTs, however, may not be applicable in all circumstances and, therefore, hybrid approaches are also

likely to be implemented. Full transition to DCTs may not be immediately possible as some methods discussed in this review need further validation before their widespread application in trials. However, these are times of great opportunities to adjust and improve clinical trials to better serve our patients.

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