SOCIOECONOMIC DETERMINANTS OF QUALITY OF CARE AND OUTCOMES IN MULTIPLE SCLEROSIS

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Socioeconomic determinants of quality of care and outcomes in multiple sclerosis
Thesis for Doctoral Degree (Ph.D.)

By

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To my baby brother William. I’m sorry I made you read the dedication page of Dad’s thesis when you were a toddler. I thought it’d be hilarious to point out that your name wasn’t on it (since you hadn’t been born – but you didn’t know that). You cried inconsolably, mum was furious. I’ve felt guilty ever since. Anyway, this one’s for you.
Popular science summary of the thesis

Multiple sclerosis, a chronic inflammatory disease of the brain and spinal cord, affects 2.5 million people worldwide and is a leading cause of neurological disability in young adults. There are Swedish and international guidelines and quality standards for providing healthcare for people living with multiple sclerosis, however, it is not known whether these recommendations are effective. This thesis explores whether the quality-of-care recommendations in these guidelines appear to improve patient outcomes, whether patients’ sociodemographic characteristics affect the quality of care they receive, and how these characteristics themselves may affect patient outcomes.

In this thesis, we show that guideline recommendations regarding frequency of neurologist visits, frequency of MRI scans, and timeliness of treatment, do seem to influence symptoms and disability for people living with the relapsing subtype of multiple sclerosis, but not for those with the progressive subtype. Importantly, we show that socioeconomic status is a strong predictor of future health outcomes for all people living with multiple sclerosis. People who were more educated, highly paid, non-divorced and White had a more favourable outcome compared to people who were less privileged. We also show that education and income had only a small influence on quality of care received, while race played a large role, with Black people experiencing significantly longer delays to receiving treatment.

We conclude that quality of care matters for achieving better outcomes for people living with multiple sclerosis; we recommend equitable care to be an additional quality benchmark to ensure the most vulnerable populations are adequately supported.
Abstract

Background

Multiple sclerosis (MS) is a chronic, inflammatory disease affecting the central nervous system (CNS), leading to varying degrees of neurological disability. While disease-modifying treatment (DMT) can ameliorate the severity of certain subtypes of this heterogeneous disease, recent research has increasingly focused on understanding other factors influencing MS outcomes. Two such factors are explored in this thesis: quality of MS care, and sociodemographic status.

Aims and Hypotheses

This thesis aims to explore the relationship between social determinants of health, quality of care (QoC) and MS outcomes in a universal healthcare context. It hypothesises that:

1. Higher quality of clinical care, including earlier initiation of DMT, is associated with more favourable clinical and patient-reported outcomes;
2. Socioeconomic status influences the quality of MS care received, as well as MS outcomes;
3. Race is associated with disparities in treatment and disability severity among people living with MS.

Materials and Methods

This research comprises a series of observational studies using data from the Swedish MS Registry, linked with national administrative and healthcare databases, and a cross-sectional observational study conducted in a tertiary hospital in the United Kingdom (UK).

Study 1 and Study 2 used longitudinal data from the Swedish MS Registry to explore the relationship between QoC indicators and patient outcomes. Study 1 assessed the effectiveness of early treatment – a QoC indicator – in improving symptoms and quality of life of people living with relapsing-remitting MS, while study 2 explored whether clinics’ performance on quality indicators set by the
Swedish MS society guidelines – including treatment timeliness, outpatient visit frequency, Magnetic Resonance Imaging (MRI) frequency, and completeness of data entry – correlated with clinical and patient-reported outcomes in people with relapsing and progressive subtypes of disease.

Study 3 used data from the Swedish MS Registry linked to national administrative databases to explore whether sociodemographic factors prior to disease onset – such as educational attainment, income, and marital status – are associated with future severity of disability and symptoms of MS.

Study 4 compared the quality of MS care received by individuals of differing socioeconomic statuses within Sweden’s universal healthcare system. We measured patients’ time from disease onset to diagnosis, time from diagnosis to treatment initiation, frequency of neurology clinic visits, and the number of MRI scans conducted within the first four years post-diagnosis. These indicators were analysed in relation to premorbid educational attainment and income levels.

Study 5 utilised cross-sectional data from a major tertiary hospital in London. It explored the relationship between race, disease severity and treatment intensity within a nominally equitable healthcare system.

All studies included both descriptive and multivariable analyses, as well as causal methodologies when comparing binary treatment exposures.

**Results**

Studies 1 and 2 revealed that QoC was associated with clinical and patient-reported outcomes in relapse-onset but not progressive-onset MS. Early DMT initiation was significantly associated with lower clinical disability as well as lower physical and psychological symptom burden, though overall quality of life was unaffected. More frequent clinic visits and MRI scans also appeared to correlate to physical health outcomes in people with relapse-onset MS.

Study 3 found that higher premorbid educational attainment and income were both associated with significantly more favourable disability scores and symptoms. Single people and married/partnered people experienced comparable disease severity, while people who underwent marital separation prior to disease onset experienced significantly worse outcomes.
Study 4 found that people with higher premorbid income had a faster time from diagnosis to DMT start, while those with higher educational attainment had a higher visit and MRI frequency in the first four years from diagnosis.

Study 5 found significant racial disparities in a contemporary cohort of people with MS in the UK, with Black and Asian people experiencing worse disability outcomes compared to White people. Black people faced longer delays in receiving their first DMT and spent a smaller proportion of their disease duration on treatment compared to White people.

Conclusions

The findings from these studies collectively indicate that both healthcare and sociodemographic factors significantly influence outcomes of MS patients. Early intervention and sustained, high-quality healthcare are crucial for improving patient outcomes. However, MS outcomes are not only influenced by healthcare factors, but also by socioeconomic status, marital status and race. This highlights the need for strategies beyond affordable healthcare in order to achieve health equity, such as cultural competency, enhanced support and outreach for vulnerable patients, and future research to understand the mechanisms through which these disparities occur. Holistic MS management must consider not just clinical, but also social determinants of health.
List of scientific papers


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<tbody>
<tr>
<td>ARR</td>
<td>Annualised Relapse Rate</td>
</tr>
<tr>
<td>BAME</td>
<td>Black and Minority Ethnic</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>DMT</td>
<td>Disease Modifying Therapy</td>
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<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
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<tr>
<td>EQ5D</td>
<td>EuroQoL 5-Dimension</td>
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<tr>
<td>MS</td>
<td>Multiple Sclerosis</td>
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<tr>
<td>MSIS-29</td>
<td>Multiple Sclerosis Impact Scale–29 item</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>PITMS</td>
<td>Predicting Individual Treatment Response in Multiple Sclerosis (patient cohort)</td>
</tr>
<tr>
<td>PROM</td>
<td>Patient Reported Outcome Measure</td>
</tr>
<tr>
<td>pwMS</td>
<td>People with Multiple Sclerosis</td>
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<tr>
<td>QoC</td>
<td>Quality of Care</td>
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<tr>
<td>UHC</td>
<td>Universal Health Care</td>
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<td>UK</td>
<td>United Kingdom</td>
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1 Introduction

A dissertation on multiple sclerosis (MS) typically begins with a statement about it being the most common nontraumatic cause of neurological disability in young people. While this ubiquitous factoid is unsubstantiated (with stroke affecting 5.4 million younger adults worldwide\(^1\), idiopathic epilepsy and migraine even more\(^2\)), it is true that for those who live with this condition, and for those who treat it, the foremost goal is to minimise disability and its consequences for patients and society.

1.1 A primer on multiple sclerosis: Clinicopathological aspects

Multiple sclerosis is a supposedly autoimmune condition of the central nervous system (CNS). The aetiology and pathogenesis are outside of the scope of this dissertation; however, the dominant hypothesis is that MS is a rare and aberrant immune response to the Epstein Barr virus\(^3,4\) that occurs in susceptible individuals, with multiple genetic and environmental risk factors contributing to susceptibility\(^5-7\).

There are two main clinicopathological components to this disease. The first is focal inflammation, occurring primarily as discrete plaques of inflammatory demyelination in the CNS white matter\(^8\). Plaques may manifest with focal neurological symptoms, often referred to as a bout or relapse, which may improve with remission of inflammation and possible remyelination and repair\(^8\). Any function of the CNS may be affected. Whether a plaque causes neurological symptoms depends partly on its location, with critical locations such as brainstem, optic nerve and spinal cord frequently causing overt sensory, motor, or visual symptoms, while lesions in non-eloquent pathways, such as associative networks, often causing no or non-localising symptoms\(^9\).

The second clinicopathological component of MS is neurodegeneration, often conceptualised as accelerated brain aging\(^8\). Radiologically and pathologically, this is characterised by faster brain atrophy compared to population controls\(^10,11\). Clinically this manifests as insidious worsening of existing disability; or at an earlier stage, may have more subtle correlates such as cognitive difficulties or inferior academic attainment compared to population controls.
Traditionally, clinically definite MS has been arbitrarily classified as relapsing-remitting or progressive\(^{12}\), depending on whether the dominant clinical presentation appears to be due to focal inflammation—causing discrete episodes of focal neurological disability followed by improvement—or neurodegeneration, with insidious disability worsening without improvement. Most (85–90\%) of cases initially present as a relapsing-remitting phenotype (referred to as relapsing-remitting MS) with eventual transition to a progressive phenotype (referred to as secondary progressive MS), while the remainder present with a progressive phenotype from onset (primary progressive MS)\(^{12}\). In reality, both processes occur simultaneously to varying degrees. Inflammation is most prominent at younger age or earlier in the disease course, with the frequency of new focal inflammation decreasing over time\(^{9,13}\). Neurodegeneration and atrophy occur throughout the entire disease course, detectable even at onset\(^{14}\); however, it is often minimally symptomatic in early stages due to higher structural and functional brain reserve in younger people\(^{15,16}\).

**Figure 1** Serial MRI in a patient with relapsing-remitting multiple sclerosis

Serial MRI in a patient with relapsing-remitting multiple sclerosis. Proton-density weighted MRI scans obtained at a | baseline, and b | 1 year, c | 2 years and d | 3 years later. Disease progression can clearly be seen in the form of new and enlarging focal lesions over time, shown here as hyperintensities (white spots).


The two processes of inflammation and neurodegeneration are not entirely independent, as inflammation, through demyelination and axonal loss, can cause
Secondary neurodegeneration\textsuperscript{9,18}. Primary and secondary neurodegeneration is felt to be the main driver of irreversible disability accumulation in multiple sclerosis\textsuperscript{10,19,20}.

Additional pathophysiological processes include slow expansion of existing lesions and establishment of tertiary meningeal lymphoid follicles, causing chronic low-grade inflammation through activation of resident CNS lymphoid cells. In contrast to acute, transient focal inflammation, this chronic inflammation is more resistant to immunosuppressive therapy, and independently contributes to neurodegeneration and disability accumulation\textsuperscript{21,22}.

1.2 Treatment of multiple sclerosis

The last 30 years has seen rapid progress in drug development for MS. There are presently 17 European Medical Agency–licenced disease modifying therapies (DMTs)\textsuperscript{23}. To date, the successful therapies have been immunomodulatory or immunosuppressive, targeting the inflammatory component of the disease. This has little effect on primary neurodegeneration, although secondary neurodegeneration is felt to be modifiable through prevention of primary neuroinflammation\textsuperscript{23}.

MS neurologists have historically been conservative in handing out immunosuppression\textsuperscript{24}, but because the disease is most inflammatory in its early stages, recent studies have shown early, proactive treatment with high-efficacy immunosuppression is more effective in mitigating long term disability compared to a more conservative approach\textsuperscript{25–27}. Earlier treatment is more effective than later treatment. This has led to a change in standards for multiple sclerosis management, with emphasis placed on rapid referral, diagnosis, and treatment initiation\textsuperscript{28}.

Aside from immunosuppression, other approaches have yielded little success in modifying long-term disability outcomes. These include remyelination therapies\textsuperscript{29}, diet\textsuperscript{30} and exercise interventions, rehabilitation\textsuperscript{31}, and attempts at neuroregeneration\textsuperscript{23}. DMT thus remains the cornerstone of MS treatment, with other supportive and symptomatic interventions designed to alleviate symptoms, but without evidenced effect on disease course.
1.3 Outcomes

Research and clinical practice have traditionally emphasised clinical and radiological metrics for measuring MS severity; this is also reflected in FDA and EMA stipulations for such endpoints for regulatory approval. Both agencies increasingly recognise the importance of patient reported outcomes; however, they are not necessary nor sufficient for regulatory approval.

*Annualised relapse rate (ARR)*

The ARR measures the number of clinical relapses experienced by a patient in a 12 month period. This was widely adopted as a primary trial endpoint for assessing treatment efficacy, relevant mainly to the relapsing phenotype, particularly in the early phase of the disease when relapses are most frequent. It is less relevant to people in later disease or with progressive forms of disease.

*Expanded Disability Status Scale (EDSS)*

EDSS remains the most widely used scoring system for quantifying MS clinical disability. The overall score is calculated from seven functional systems scores pertaining to visual, brainstem, pyramidal, sensory, cerebellar, sphincteric and cerebral function, in addition to an ambulation score. Scores range from 0 (normal neurological examination and no disability) to 10 (death due to MS), incrementing in steps of 0.5 (except between 0 and 1) that reflect increasing levels of disability on clinical examination. There are many points of critique to this scale, including its ordinal non-normal (often bimodal) distribution, non-uniform step size, the over-representation of mobility in the scale at the cost of nonmotor functions, and variable inter-rater reliability, it has nonetheless stood the test of time as the most commonly used outcome measure for MS research and clinical practice.

*MRI Metrics*

The radiographic hallmark of MS is the T2 hyperintense white matter lesion representing a demyelinated plaque. MRI metrics of disease activity include lesion number, presence/number of new or enlarging lesions, presence/number of active contrast-enhancing lesions, and total lesion volume. Though not specific to MS, additional metrics of neurodegeneration include measures of brain volume or atrophy. MRI metrics are used clinically for diagnosis and monitoring disease activity or response to therapy; however, there is poor correlation between these metrics and clinical disability, referred to as the
clinico–radiological paradox\textsuperscript{37–40}. More advanced metrics using MRI sequences beyond standard clinical protocols are used in research, primarily to explore pathophysiological mechanisms of the disease, including detailed assessments of white matter tract integrity, myelin density, brain metabolism, functional connectivity, microstructural changes, and iron deposition, providing deeper insights beyond what standard clinical sequences reveal about lesion presence and load\textsuperscript{41,42}.

\textit{Patient Reported Outcome Measures (PROMs)}

PROMs capture a person’s subjective experience of their symptom burden, functioning, and quality of life. Many disease–specific and disease–invariant instruments exist. Common instruments used in MS research include the MS Impact Scale (MSIS–29)\textsuperscript{43}, the MS Quality of Life–54 (MSQoL–54), and the disease–invariant EuroQOL 5–Dimensional Quality of Life questionnaire\textsuperscript{45} (EQ5D). Within these instruments, outcomes may be divided into specific domains such as physical vs psychological symptom burden, domains of functioning (such as mobility, pain, self–care, cognition or sexual function), or global ratings of wellbeing. Targeted PROM instruments measure specific domains of symptomatology and impairment, such as fatigue, mood or work productivity.

1.4 Prognostic factors

On clinical outcomes such as disability scores and radiological metrics, MS is a progressive disease\textsuperscript{46–48}. While EDSS can fluctuate, particularly during a relapsing disease course, the overall trend is for EDSS worsening with greater disease duration\textsuperscript{49}. However, many patient, disease, and healthcare factors are known to affect prognosis\textsuperscript{50}. The two main patient factors considered to affect disability progression are age at onset and sex. Typically, later onset age is associated with a more rapid decline – however, as patients with earlier onset disease necessarily have a longer disease duration at a given age, the opposite pattern is true when age–adjusted disability is the outcome measure – with earlier onset age being associated with higher age–adjusted disability\textsuperscript{48}. Although MS is more common in females, males experience faster disability accumulation and are more likely to be diagnosed with progressive–onset disease, which carries a less favourable prognosis compared to relapsing–onset disease course\textsuperscript{50,51}. Other disease factors also play an important role. Patients with a higher number of
lesions on MRI and intrathecal production of IgG, IgM and kappa light chain antibodies at diagnosis have a poorer prognosis as measured by time to first relapse or disability progression episode\textsuperscript{52–54}. For patients with treatment–eligible disease (those with relapsing MS, or progressive MS with evidence of focal inflammation), healthcare factors such as the timing of DMT initiation, the efficacy of the chosen DMT, and treatment persistence also influence outcomes\textsuperscript{28,50}.

MS outcomes research focuses heavily on traditional prognostic markers of disease severity such as radiological and wet biomarkers, as well as the effect of DMT or other potential therapeutic agents. Other possible factors influencing MS outcome have received less attention. This thesis explores two such factors that have implications for practicing clinicians.

1. Does quality of care (QoC) affect MS outcomes?

   Swedish national QoC guidelines (Svenska Multipel Skleros Sällskapet\textsuperscript{55}), published in 2016, have sought to standardise the care received by people with multiple sclerosis (pwMS). These guidelines, arrived at through expert opinion, include a wider scope of directive, quantitative benchmarks compared to other evidence–based guidelines (American Academy of Neurology\textsuperscript{56}, NICE\textsuperscript{57}, and international consortia\textsuperscript{58,59}). Studies 1–2 of this thesis aim to explore the relationship between QoC and patient outcomes.

2. Does sociodemographic status affect MS outcomes and quality of MS care?

   While the importance of social determinants of health has long been recognised in other diseases, it has only recently gained attention as a possible prognostic marker in MS. In studies, 3–5, we explore the role of sociodemographic status – both as a predictor of health outcomes and as a predictor of QoC received.
2 Literature review

This review summarises the background for the doctoral project “Socioeconomic determinants of QoC and outcomes in multiple sclerosis”. It is divided into two parts. The first examines the evidence connecting QoC to MS outcomes, in the context of the Swedish MS Society guidelines. The second examines whether the QoC, and subsequently MS outcomes, is influenced by sociodemographic status.

Part I: Summary of quality metrics related to national quality of care guidelines, and the evidence/justification underlying these.

The Swedish MS society (Svenska MS Sällskapet) in 2009 published the first national quality guidelines for the care of pwMS, with its most recent edition in 2016 harmonised with the Ministry of Health and Social Welfare guidelines for MS care\textsuperscript{60}. Below is a summary of the main recommendations (paraphrased in English for brevity) and a review of evidence supporting them.

2.1 Visit frequency and documentation

1. For quality assurance of MS care, a minimum yearly visit is recommended for documentation of a minimal dataset in the Swedish MS registry. This includes: current treatment, number of relapses in the previous year, current EDSS, systematic assessment of MS symptoms, secondary progression, MRIs performed in the previous year and relevant results, and capacity to work (or disability support services required).

i. All persons with MS shall be offered at least an annual visit for documentation of their medical and rehabilitation requirements.

ii. At least 90\% of MS patients within any given neurology clinic should have complete annual visit documentation according to above requirements.
This recommendation is in agreement with other consensus expert opinions regarding what constitutes “quality care”\textsuperscript{57–59,61}, some of which suggest even higher visit density than annual. For example, an international consensus panel stipulated that while the minimum standard of annual visits is reasonable, an aspirational and achievable target should be 6-monthly visits. There is no direct evidence that more frequent visits improve outcomes. A surveillance review of the NICE guidelines in 2018 (which also advocates for a 12-monthly comprehensive review) identified no supporting evidence for this recommendation from literature, however, it is self-evident that visits enable disease activity and DMT safety to be monitored. There is direct evidence that the presence of residual disease activity while under treatment with a DMT is associated with worse clinical disability\textsuperscript{62,63}, and that patients switching treatment can have more favourable outcomes if switched to a higher-efficacy class compared to another drug of similar efficacy\textsuperscript{64–66}. There is no universally accepted clinical threshold at which this should take place, and as such, current guidelines (e.g. Canadian\textsuperscript{67} guidelines), MS coalition of the USA consensus\textsuperscript{68} paper, Association of British Neurologists 2015\textsuperscript{69} guidelines, NICE guidelines\textsuperscript{57}) are based on expert opinion rather than direct evidence.

\begin{itemize}
\item[i.] Årsbesök: För att kunna utvärdera definierade kvalitetsvariable (se nedan) registreras ett “årsbesök” med följande ”minimal dataset”:
\begin{itemize}
\item Aktuell behandling
\item Antal skov senaste året
\item Aktuellt EDSS
\item Systematisk genomgång av MS-relaterade symptom, t ex via MS-kollen
\item Registrering avseende övergång i SP fas eller inte
\item Registrering av genomförda MR-undersökningar och införande av relevanta data
\item Inventering av aktuell arbetsförmåga, ev ersättningsförmåa mm
\end{itemize}
\item[ii.] Basdata: I SMSreg registreras basdata rörande genomförd diagnostisk utredning, debutår, föroloppstyp samt tid då patienten blev känd på neurologkliniken.
\end{itemize}

\textit{Svenningson, A. Kvalitetssäkring av MS-vården i Sverige. Svenska MS Sällskapet 2016}
2.2 Access to workup, diagnosis, and management

2. The time from referral of suspected MS, to comprehensive workup, diagnosis and management, should be as short as possible.
   i. Referral date to first DMT should be 3 months or less.
   ii. Time between first clinical symptom of MS to diagnosis should be as short as possible, but given a period of this time is outside of the control of neurology clinics, there is no stipulated goal for this.

3. All MS patients should have access to rehabilitation and multidisciplinary allied health services; however, the appropriate parameters for this quality metric are still under development.

Svenningson, A. Kvalitetssäkring av MS-vården i Sverige. Svenska MS Sällskapet 2016
There is variable evidence supporting efficacy of rehabilitation in improving clinical and patient reported outcomes. Khan and colleagues have summarised the most pertinent points in a systematic review. This subject is not in the scope of the doctoral project and will not be reviewed.

**2.3 Medical quality goals**

4. **Treatment frequency**: adequate medical treatment shall be offered to patients where there is medical evidence for its effectiveness. This means that measures of proportion of patients who receive treatment within certain defined patient groups can be used as quality measure.
   
   i. **Relapse onset MS**: Initiation of treatment should occur in >90% of those with clinically isolated syndrome [the first occurrence of MS-like symptoms but not fulfilling diagnostic criteria for clinically definite MS] and early relapsing MS [NB: no definition of early relapsing MS given here]. For all patients with relapsing MS less than 60 years of age and with disease duration of less than 15 years, at least 80% should be treated with disease modifying therapy.

   ii. **Progressive MS**: Those patients without signs of inflammatory activity (relapses or gadolinium enhancing MRI lesions) should not be treated. No evidence-based treatment target is defined for this goal.
The notion of continuing therapy as far as indicated is common practice in the clinical community and supported in consensus statements (e.g. the position statement article “Time matters in Multiple Sclerosis” by Giovannoni and colleagues\textsuperscript{75} includes recommendations to “maintain DMT early and for as long as patient is at risk of inflammatory disease” and “minimise treatment gaps”). There have been no trials of differing proportion of time on treatment as the main variable of interest; however, in delay-start trials and observational studies, there is inherent collinearity in earlier time to treatment initiation and greater proportion of time on treatment; thus, the two effects cannot be disentangled. There is, however, evidence that pauses in treatment during the inflammatory phase of the disease can lead to treatment rebound, particularly in lymphocyte sequestering/compartmentalising preparations\textsuperscript{76–79} (compared to cytotoxic or immunomodulatory preparations). Furthermore, due to lack of evidence-based stopping criteria for DMTs\textsuperscript{80} and conflicting evidence for their utility in older age\textsuperscript{81,82} and later stages of disease\textsuperscript{83,84}, the quality goal to
persist with treatment in <60 year olds with <15 years duration is commonly accepted. A recent randomised noninferiority trial of stopping DMT in persons >55 years of age and stable disease was inconclusive.

5. **Relapse frequency as measure of disease activity: one should strive for the lowest possible relapse frequency with the safest possible treatment.**
   i. **Target for relapse rate, in relapsing MS, using the most effective available treatment, is <0.2 relapses per year (with disease duration <15 years)**

   Skov som mätt på sjukdomsaktivitet: Lågsta möjliga skovfrekvens med säkrast möjliga behandling eftersträvas.
   i. Skovfrekvens kan mätas i SMSreg på individnivå och gruppnivå.
      - Målverde: Riktmärke för målverde är den skovfrekvens som konsekvent uppnås med den idag mest effektiva tillgängliga behandlingen (≤ 0,20 skov per år) beräknat på RRMS < 15 års sjudomsduration.

   Svenningson, A. Kvalitetssäkring av MS-vården i Sverige. Svenska MS Sällskapet 2016

   The minimisation of relapse activity for prevention of disability and progression is a central tenet of MS treatment but the relapse rate itself is a target of the other quality measures in this guideline (e.g. early commencement of DMTs and continuation of DMTs) rather than an action in its own right. This doctoral project does not study relapse rate as a quality measure.

6. **MRI changes: DMTs have a well-documented effect on typical MRI markers of MS; these can thus be used as a measure of effectiveness of a given DMT. There is also correlation between MRI changes and various types of MS disease activity such as relapses and disease progression. To monitor subclinical disease activity, the Swedish MS society believes it is justified to monitor with cranial MRI at least annually during the disease’s inflammatory phase.**
   i. **Quality target: striving for minimum possible progression of MRI changes (including new/enhancing T2 lesions, “black holes”, T2 lesion load and brain volume). At least 80% of all patients with relapsing MS under 60 years of age should have undergone an MRI in the last 2 years. Patients in the progressive phase with ongoing inflammatory activity shall also adhere to the above.**

   Svenningson, A. Kvalitetssäkring av MS-vården i Sverige. Svenska MS Sällskapet 2016
The Swedish MS society guidelines are similar but not identical to guidelines published by other national international guidelines. Elsewhere, more specific indications for MRI frequency are given based on MS course, phase of disease and specific treatment monitoring requirements. Both European consortia (MAGNIMS – Magnetic Resonance Imaging in MS) as well as the Swedish neuroradiology society suggest at least 2 baseline MRIs: At least one for diagnosis, as well as a re-baselining MRI 6 months after commencement of a disease-modifying therapy. For routine follow-up, two MRIs are recommended within 12 months of diagnosis, and at least annual routine follow-up MRIs thereafter. For every treatment switch, a re-baselining MRI is recommended shortly after commencement of the switch therapy. Symptoms suggestive of a true relapse justify additional MRIs for monitoring of disease activity. For those patients receiving treatments that increase their risk of progressive multifocal leukoencephalopathy (a potentially fatal opportunistic CNS infection caused by reactivation of John Cunningham Virus during states of decreased CNS immune surveillance, as is the case with certain DMTs), any suggestive symptoms justify additional MRI for monitoring.

The role of MRI for diagnosis, early prognostication and monitoring of disease activity is well established as is its utility in early diagnosis of progressive multifocal leukoencephalopathy. The evidence for each of

Svenningson, A. Kvalitetssäkring av MS-vården i Sverige. Svenska MS Sällskapet 2016
these indications is vast, but are summarised accordingly in each guideline as the justification for each recommendation.

The Swedish guideline’s recommendation of at least one routine MRI every two years in relapsing MS is presumably based on the much higher sensitivity to disease activity compared to clinical monitoring alone\textsuperscript{75,90}. In spite of this, there is no consensus regarding how the presence of subclinical MRI activity should be acted upon, and how this information should be combined with clinical findings to inform treatment decisions\textsuperscript{75}. The effect of MRI frequency itself on long term clinical outcomes is not known.

Part II: Relationship between sociodemographic characteristics, quality of care and health outcomes

2.4 Socioeconomic predictors of healthcare utilisation

Socioeconomic status has been implicated as a major predictor of healthcare utilisation. Poorer health status and lower socioeconomic status are associated, with possible bidirectional causality\textsuperscript{91,92}. The greater overall volume of healthcare utilisation by low socioeconomic groups thus may not indicate higher quality care, but rather indication bias. Conversely, specific services such as specialist visits are utilised more often by persons with higher socioeconomic status and/or better health states. There are no studies that specifically address socioeconomic factors associated with volume of MS care in a universal healthcare (UHC) system. There are, however, ample studies that examine socioeconomic factors associated with access to primary and specialist care, including for patients with chronic diseases, in countries with UHC.

A study directly relevant to the doctoral project examined linked registry data for 34707 adults in Stockholm county during years 2006–2007\textsuperscript{93}. Income quintiles correlated to probability and volume of outpatient visits. In unadjusted analyses, those with lower income had a higher volume of outpatient utilisation. After adjusting for health status, higher income groups had 11–49% more outpatient visits compared to those with the lowest level of income. Moreover, the distribution of generalist vs specialist visit frequency indicates those with higher income are utilising more specialist care, including private specialists.
This pattern is consistent across studies outside of Sweden. In the Netherlands, lower income or education corresponded to 50–150% higher healthcare expenditure; however, this was almost entirely accounted for by taking physical and mental health states into consideration\textsuperscript{94}. This again indicates that higher healthcare utilisation in lower socioeconomic groups is a result of indication bias rather than better access to care. In addition, numerous studies in Europe and Canada demonstrate those with higher education, occupational class or income had greater utilisation of specialist care, after adjusting for health states including amongst persons with chronic disease\textsuperscript{95–99}. 

The relationship between socioeconomic factors and \textit{timeliness} of initial diagnosis and/or treatment has been studied in a number of diseases including MS, only some of which were conducted in UHC contexts. In a review of socioeconomic predictors of melanoma stage at diagnosis, those with lower income or education tended to have more advanced disease; this was attributed to poorer health literacy or higher threshold for seeking care due to affordability, however, not all reviewed studies were within a UHC context\textsuperscript{100}. In Alzheimer’s disease in a UHC setting, higher socioeconomic status was associated with first clinic visit at an earlier disease stage\textsuperscript{101}. In the MS setting within a UHC context, delay to second-line treatment was longer for patients from more deprived areas who had remained on first line therapy for more than 5 years in rural France\textsuperscript{102}. Numerous studies indicating strong socioeconomic predictors of accessing timely and high-efﬁcacy treatments have been conducted in user-pays contexts but are not relevant to this doctoral work.

\section*{2.5 The study of race in medicine – a historical context}

Race is a construct that was historically afforded scientific legitimacy as essential variants of the human species. The groundwork for scientific racism was laid by Carl Linnaeus’s \textit{Systema Naturae}\textsuperscript{103,104} (1735), which classified humans into four variants: “\textit{Europaeus albus, Americanus rubescens, Asiaticus fuscus, and Africanus niger}”, ranking them by attributes—with White European traits (‘light, wise, inventors’) deemed most desirable and Black African traits (‘sly, sluggish, neglectful’) the least\textsuperscript{105}. Regrettably, this concept of biological determinism was subsequently weaponised through history to justify atrocities such as slavery, colonialism, and the Holocaust. Its influence on medical science is profound, demonstrated even today by the differential treatment of racial
groups based on beliefs about essential biological or genetic differences\textsuperscript{106,107}. This includes beliefs about multiple sclerosis being rare and more severe in Black people\textsuperscript{108--110}. These beliefs are unfounded, with vanishingly few exceptions. Research shows there is far greater genetic variation within so-called racial groups than between them\textsuperscript{111}. Today, most scientists and scholars understand race as a social construct with no biological basis\textsuperscript{112,113}. The disparities observed across nearly all societal measures today predominantly result from systemic racism and its socioeconomic impacts, rather than from inherent biological differences.

The role of race in contemporary healthcare and health outcomes is highly context-dependent. The UK, despite its extensive history of colonialism and involvement in the slave trade, has only a short (post WWII) immigration history of predominantly skilled, paid workers. This contrasts with the United States, where a longer history of slavery and constitutionally enshrined racial segregation, coupled with lower social welfare, creates distinct societal dynamics. While QoC and health outcomes in the United States often fall along racial and socioeconomic lines\textsuperscript{114}, such disparities in the UK are less pronounced. Unlike the UK, most other high-income social democracies do not systematically collect race-based data. As such, the review focuses on data from the UK.

The terms race and ethnicity, while often used interchangeably, have distinct connotations. In this dissertation, ethnicity refers to one’s cultural identity (and can be independent of race, for example, Hispanic or LatinX), whereas race refers to external categorisation based on physical characteristics or presumed ancestral origins\textsuperscript{115}.

### 2.6 Race and quality of care

The relationship between race and QoC is not a uniform picture in the UK. In view of decades-long initiatives that have specifically sought to achieve health equity in disadvantaged groups, racial minoritisation is not always associated with lower QoC within targeted disease groups; moreover, lower QoC does not always imply worse outcomes\textsuperscript{116,117}.

Three disease areas exemplify this: cardiovascular disease, diabetes and cancer\textsuperscript{117}.
In cardiovascular disease, South Asian groups have superior QoC and outcomes compared to other race groups despite having an increased risk of coronary artery disease, stroke and diabetes. Conversely, Black groups also have higher incidence of stroke but receive lower quality of cardiovascular care, including poorer access to care, lower rates of drug prescriptions, less monitoring, and poorer achievement of treatment targets compared to other race groups\textsuperscript{118,119}.

In cancer, black and minority ethnic (BAME) groups have lower uptake of routine cancer screening. Historically, stage at diagnosis was overall higher for Black Caribbean people compared to White British people, but this has minimised or equalised across race groups for most cancer types since 2017. The exceptions are higher rates of late-stage breast, ovarian, uterine and colon cancer diagnoses in Black and Asian women, yet lower rates of late-stage prostate cancer diagnoses in Black men. Cancer mortality rates are similar or lower in BAME groups compared to White groups, except higher prostate cancer mortality in Black males despite lower rates of late-stage diagnoses.

In diabetes care, Black and South Asian groups initiated diabetes treatment faster than White groups\textsuperscript{120}. This has been attributed to higher prevalence and community awareness in these groups, as well as general practitioner incentive programs for equitable and standardised QoC. However, subsequent long-term care was inferior in BAME groups compared to White groups\textsuperscript{120}. Outcomes including diabetic complications and mortality were mixed within and between groups, due to biological, lifestyle and socioeconomic factors\textsuperscript{121}.

2.7 Race and health outcomes

Race and general health outcomes in the UK

The intersectionality of race, socioeconomic status and health outcomes is also complex. Health outcomes aligning with socioeconomic gradients are seen overall, and within race groups\textsuperscript{122,123}. Differences in socioeconomic status and health outcomes between race groups, however, are highly variable. White and Mixed groups had the lowest overall life expectancy despite enjoying the highest (or next-highest) socioeconomic privilege and overall quality of life\textsuperscript{177,124}. This paradox is partly attributed to the healthy migrant effect, as well as differences in risk exposure profile, with white men and women having the highest rates of alcohol and tobacco use compared to other groups\textsuperscript{122}.
Overall, Black and Mixed Black groups suffer more socioeconomic deprivation, higher number of long-term health conditions, lower life satisfaction and health related quality of life compared to the reference White British group\textsuperscript{125,126}.

There is greater heterogeneity in outcomes in the Asian group, with people of Indian and Chinese ethnicity broadly enjoying equal or more favourable socioeconomic advantage and health outcomes (both subjective and objective) compared to the reference White British population, while people of Pakistani or Bangladeshi ethnicity are often in the most disadvantaged position on objective and subjective outcome metrics\textsuperscript{126}.

**Race and MS outcomes**

In user-pays systems such as the USA, racially and ethnically minoritised persons experience faster MS disease progression compared to white persons; however, race and ethnicity correlates to access to and QoC in such settings and cannot be extrapolated to contexts of theoretically equitable care\textsuperscript{109}. For example, disease severity of Black pwMS did not differ from age- and sex-matched White pwMS in Canada\textsuperscript{127}.

Most studies performed in UHC contexts do not directly record race but country of birth, which limits study to first generation migrants and captures a period of differential exposures between origin and destination countries. For example, a French population registry study demonstrated a more severe course in pwMS born in North Africa compared to French Caucasians\textsuperscript{128}, and the authors implicated genetics as being a determinant (without having included genetics in the study).

Only one study from the UK examined the role of ethnicity. This study descriptively compared MS outcomes in 43 White British pwMS and 43 Black Caribbean pwMS, finding duration-adjusted disease severity (as measured by the MS severity scale) was higher among Black Caribbean pwMS in unadjusted analyses\textsuperscript{129}. To my knowledge, there are no studies on racial disparities in MS QoC in a UHC context.
3 Research aims

A UHC system has theoretically equitable access to medically necessary care, regardless of social demography or ability to pay. As a single payer system with finite resources, resource expenditure must be justified by its effectiveness. In this thesis, two studies investigate the effectiveness of MS QoC recommendations. Importantly, we explore both clinical and patient–reported outcomes, recognising the importance of patients’ subjective experiences in guiding health policy and clinical decision making. Next, we explore the notion that UHC may not reach all recipients equally. Three studies explore the role of socioeconomic status, including race, in both QoC and MS outcomes.

In Study 1, we investigate whether an evidence–based recommendation of early treatment, known to improve clinical disability, is also associated with more favourable patient–reported outcomes.

In Study 2, we describe Swedish neurology clinics’ performance in four QoC indicators, and model the relationship between each indicator and patient outcomes. These four indicators included three that did not have prior empirical evidence for effectiveness, as well as one evidence–based positive control.

Study 3 explores the relationship between sociodemographic characteristics prior to MS onset – such as educational attainment, income, and marital status – and future MS severity as measured by clinical and patient–reported outcomes.

Study 4 assesses whether higher socioeconomic status is associated with better QoC in Swedish MS clinics.

In study 5, using a UK single centre cohort, we investigate whether there are racial disparities in treatment intensity and disability outcomes among pwMS.
4 Materials and Methods

4.1 Data Sources

Swedish National Registers

Sweden’s national healthcare and demographic registers provide a system of data resources that can be integrated for epidemiological research. These registers are linked through a unique ten-digit Swedish social security number (Swedish: personnummer) given to every Swedish resident, enabling compilation of longitudinal, person-level data across health and public service data platforms.

Access to registry data, as well as linkage of data across registries, is granted only with ethical approval. Unique patient identifiers (not social security numbers) are generated with each data linkage, such that the data used in the Swedish registry-based studies are pseudoanonymised.

Swedish MS Registry:

The Swedish MS registry, part of the Neuroreg registries, serves as a national quality register for multiple sclerosis care. The registry has collected prospective data since 2001 (with retrospective data for events prior to this date). It is used as part of routine clinical care as a simple and efficient means of documentation, thus contains detailed clinical information such as dates of disease onset, diagnosis, clinic visits, relapses, MRI scans, treatment start and stop dates, and an array of clinical and patient-reported outcome variables. Patient registration is voluntary. As of 2021, it includes approximately 84% of the estimated prevalent population of pwMS\textsuperscript{130}.

National Patient Register:

The National Patient Register collects data from all in-patient (since 1987) and specialist out-patient (since 2001) visits across Sweden, excluding primary care. It includes dates of outpatient visits, admission and discharge dates, and primary
and secondary diagnoses for each episode using the Swedish International Classification of Diseases (ICD-9 and 10). Coverage and validity is high, estimated to record 99% of all episodes.

Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA):

LISA (Swedish: Longitudinell integrationsdatabas för Sjukförsäkrings- och Arbetsmarknadsstudier) was established in 1990 as a compilation of national labour market data held by Statistics Sweden and other registries. The register records annual information for all Swedish residents aged 16 and above, regarding demographics, marital status and household composition, education, income sources, and social insurance benefits.

These registers provide a comprehensive platform for conducting epidemiological studies, with a wide array of data on health, demographics, and socioeconomic factors, and served as the foundation for studies 1–4.

The PITMS cohort

The PITMS cohort (Predicting Individual Treatment Response in Multiple Sclerosis) is a UK-based multicentre observational cohort study that collects both prospective and retrospective data for treatment-eligible patients with MS across 4 university hospitals in the United Kingdom: University College Hospital, Great Ormond Street Hospital, Evelina Children’s Hospital, and Birmingham Children’s Hospital (three paediatric hospitals and one adult hospital). Inclusion criteria were people with clinically definite multiple sclerosis per 2017 McDonald criteria, who were initiating or switching to a new DMT at a participating centre between June 2019 and October 2023. Eligible patients were identified and invited for enrolment from DMT initiation clinics. Over 700 adults and 100 children have been recruited, with recruitment ongoing as part of an extension study.

For adult participants, the study schedule consisted of three core study visits at 0, 6, and 18 months relative to DMT initiation date. Each visit collected a comprehensive set of outcome measures including EDSS scores, alongside a battery of cognitive and patient-reported outcomes.
In addition, comprehensive medical and demographic data collected at the baseline visit included age, sex, race and ethnicity, comorbidities, medications, smoking, alcohol and drug history, education, employment status and type, household composition. Retrospective MS history at baseline was obtained from patient self-report and correlated with medical records, including symptom onset date, diagnosis date, DMT history including DMT type, start and stop dates, and number of relapses in the 2 years preceding the baseline visit. Patients underwent MRI of the brain and spinal cord and had serum and whole blood samples collected each visit.

**4.2 Study design**

Standard epidemiological methods were used to define meaningful cohorts and analyse the observational data, including standard methods for bias mitigation.

Below is a summary of the designs for each constituent study.

*Study 1: Association between early treatment of multiple sclerosis and patient-reported outcomes.*

**Design:** Observational, propensity matched case-control study

**Population:** Participants in Swedish MS registry with adult-onset, relapse-onset MS.

**Intervention/Exposure:** DMT commencement within 0–2 years (early) compared DMT commencement 2–4 years (late) after disease onset.

**Outcome:** Longitudinal repeated measures of patient-reported physical and psychological symptoms (measured by MSIS-29) and health-related quality of life (measured by EQ5D-3L).

**Time:** Exposure period was 0–4 years after disease onset. Follow-up period was 4–10 years after disease onset. The selected cohort had disease onset after January 2001 (which represents start of prospective data collection in Swedish MS registry) and before June 2016 (to ensure minimum 4 years follow-up time for all participants at data extraction in June 2020).

**Bias and mitigation:**
1. Indication bias. Mitigated by defining study population by propensity score matching on baseline variables. In this case, onset age, sex, EDSS and relapse rate are common factors considered when making treatment decisions regarding timing of DMT start, and are also correlated with the outcome. The main unmeasured confounder not captured in the data is MRI severity metrics at baseline; however, the direction of any residual indication bias would bias results towards a null finding – thus the true effect size may be higher than model estimates.

2. Confounding by calendar year of onset. Over the inclusion period (2001–2016), there has been temporal trend towards earlier treatment start, as well as more sensitive diagnostic criteria that include milder phenotypes with better prognosis in more recent years. Thus calendar year of onset was modelled as a clustering variable.

3. Attrition bias
   a. There is a high (approximately 50%) attrition of participants during cohort selection, due to overall low rates of data completeness during the “baseline” period, largely due to missingness of EDSS scores. As missingness of early EDSS scores is extremely common in observational MS registries, affecting both treatment and comparator groups, missingness was not judged to be informative thus complete case analysis was performed.

Study 2: Association between clinic-level quality of care and patient-level outcomes.

Design: Observational cohort study

Population: Participants in the Swedish MS registry with adult-onset MS, stratified by MS course (relapsing- or progressive-onset)

Intervention/Exposure: QoC provided at individual neurology clinics. Four metrics were assessed: 1. Number of visits per patient per year, 2. Number of MRI scans per patient per year, 3. Completeness of data entry, 4. Time from disease onset to commencement of first DMT (assessed for relapsing MS only)

Outcome: Longitudinal repeated measures of 1. Clinical disability, measured by EDSS, and 2. Patient-reported physical and psychological symptom burden, measured by MSIS-29.
Time: Exposure variables were measured during calendar year of each patient’s disease onset. Follow-up period was from disease onset until last recorded outcome measure. Dates of disease onset were restricted to after January 2005 (allowing a 4-year run-in after registry commencement, to ensure QoC measures reflected patient care rather than clinicians’ computer proficiency) and before December 2015 (to allow minimum 4 years of follow-up opportunity prior to data extraction December 2019).

Bias and mitigation:

Indication bias: Like the quality metric of “time to treatment” in study 1, overall intensiveness of care is inherently subject to indication bias. To overcome this, QoC was measured at a clinic level.

Referral bias: Systematic differences in casemix, be it due to geography (urban vs rural, high-income vs low-income catchment), clinic capacity or clinic specialty interests (e.g. academic vs community clinics), may lead to systematic differences in patient outcome between clinics. This was addressed by modelling clinics as random effects in mixed model analyses.

Confounding: We know that treatment intensity and duration affects MS outcomes. Supplementary analyses included treatment variables to ensure the estimated correlations were not due to correlation between QoC and quality of treatment.

**Study 3: Association between premorbid sociodemographic status and MS outcomes**

**Study design:** Longitudinal observational cohort study

**Population:** Participants in the Swedish MS registry with MS onset at/after working age (23–59 years).

**Intervention/Exposure:** Three sociodemographic factors: premorbid educational attainment, premorbid income, and premorbid marital status.

**Outcome:** Longitudinal repeated measures of 1. Clinical disability, measured by EDSS, and 2. Patient-reported physical and psychological symptom burden, measured by MSIS–29.
Time: Exposure variables were measured at two baseline timepoints: 1 year and 5 years prior to MS onset. Outcomes were measured between MS onset until last follow-up. Baseline timepoints were restricted to after January 2005 to allow comorbidity index calculation from the national patient registry (which records outpatient diagnoses from 2001), and prior to December 2015 to allow at least 4 years follow-up for outcome measurement prior to data extraction December 2019.

Bias and mitigation:

Reverse causation: Though the exposure occurred prior to the outcome, we are increasingly aware of an MS prodrome during which paraclinical measures such as academic performance, sickness absence and medical visits diverge from that of the healthy population in the years leading up to overt disease onset. Indeed, at diagnosis, brain volume has already diverged from the healthy population distribution. This indicates that the effects of MS may predate the onset date and have affected the exposure variables. We accounted for this by measuring the exposures 5-years prior to MS onset, along with 1-year prior.

Confounding: It is possible that an association between socioeconomic status and outcome is due to more privileged people accessing higher QoC, be it more timely treatment start or more intensive therapy. This was mitigated by adjusting for individual patient treatment parameters. The association between socioeconomic status and QoC was investigated in study 4.

Study 4: Association between socioeconomic status and quality of multiple sclerosis care in Sweden

Study design: Observational cohort study

Population: Participants in the Swedish MS registry with onset of relapsing MS during working age

Intervention/Exposure: Premorbid educational attainment, premorbid income quartile.

Outcome: Four patient-level QoC measures: onset-to-diagnosis time, diagnosis-to-treatment time, neurology clinic visit frequency and MRI visit frequency in the first 4 years since diagnosis.
Time: Exposures were measured in the calendar year prior to MS onset. Outcomes were measured after disease onset. For consistency with study 3, the same baseline calendar year selection criteria were applied.

Bias and mitigation:

Indication bias for MRI frequency and visit frequency was addressed by including two measures of disease severity (median EDSS score and ARR) as covariates.

Confounding: Place of residence was a potential confounder, with more socioeconomically privileged persons often residing in urban environments that may have greater ease of access to specialist care. This was accounted for by adjusting for urban/rural residency.

Study 5: Racial Disparities in Multiple Sclerosis Treatment and Outcomes in London, UK

Study design: Cross-sectional observational cohort study

Population: Adult participants in the PITMS cohort study. The adult cohort belonged to a single centre tertiary hospital (Queen Square MS Centre, University College Hospital, UK)

Intervention/Exposure: Race, categorised according to England and Wales census categories: White (British, Irish, Gypsy/Irish Traveller, Roma, Other), Black (Caribbean, African, Black British, Other), Asian (Indian, Pakistani, Bangladeshi, Chinese, Other), Mixed, Other (Arab, Other).

Outcome: Disability (measured by EDSS), Treatment (measured by 1. onset-to-DMT time, and 2. proportion of disease time treated with DMT).

Time: Main exposure was ascertained at time of study assessment but present throughout lifetime. Outcomes were measured cross-sectionally during the study period (June 2019–October 2023).

Bias and mitigation:

Confounding: there are frequent assumptions about socioeconomic confounders. While education has been adjusted for, income is more problematic, discussed in the Discussion section.
4.3 Outcome analyses

Mixed effects models were used for outcome analyses throughout the studies, allowing multiple levels of intra-group correlations in the response variable. Studies 1–3 included repeated outcome measures that are correlated within each patient; in addition, a higher level of clustering was used to account for dependence of outcomes from the same clinic or the same calendar year of onset. Studies 4 and 5 clustered only on calendar year of onset. With a single level of clustering, alternative methods such as generalised estimating equations could have been used to account for within-cluster correlation, but for consistency, the same methods were employed throughout.

Linear models (or in our case, linear mixed models) are limited to continuous outcomes with normal distributions. While EDSS is a 20-level ordinal variable with bimodal distribution, it is typically modelled as a continuous variable. Generalised linear mixed models extend linear mixed models to allow for non-normal and non-continuous distributions of the response variable, such as the heavily right-skewed MSIS-29, or the 3-level ordinal subscales of EQ5D-3L.

4.4 Ethical considerations

The doctoral project is ethically sound according to the declaration of Helsinki and the principles of beneficence, nonmaleficence, autonomy and justice. It aims to benefit the subjects of study without causing harm, as it uses data already collected as part of routine care, to learn about how we might improve the lives of the same people who generated that data. Participants are enrolled in the national registry after active informed consent is sought (and periodically reaffirmed, in writing), is legal, and has been approved by local ethics review boards. All patients with a diagnosis of MS in Sweden are invited to participate; the registry data captures approximately 80% of all patients with MS in Sweden. Data confidentiality and security is maintained according to GDPR and KI requirements.

Study 5 was undertaken under institutional ethical approval in the UK. As with the Swedish data, this observational study abides by the declaration of Helsinki and was performed with written, informed consent. The Participant Information
Sheet stipulated the purposes and scope of the research being undertaken with the data, including that of study 5. All data was given directly by the patients voluntarily, with the option of omitting or withdrawing data at any time. A unique aspect of the dataset for project 5 was the collection of race and ethnicity data that is not permitted in Sweden and many European countries, but a routine part of all public data collection in the UK, where collection of “protected characteristics” data (such as gender identity, religion, race/ethnicity, and sexual orientation) are used for measuring and benchmarking antidiscrimination policies. The acceptability of this is evidenced by the very low (<1%) missing data in this optional variable. The use of race data to study racial disparities in healthcare is beneficent and nonmaleficent provided the study is conducted in a culturally safe way, with patient autonomy, and conclusions are drawn appropriately as an endeavour to improve justice.

The main ethical concern is the possibility for results to be misconstrued, or for harmful conclusions to be drawn. Some may interpret longer delays to treatment or lower treatment intensity being a result of medical noncompliance or nonattendance in some racial groups, or the overall poorer outcomes in minoritised groups being due to immutable biological differences rather than a modifiable outcome, or due to confounding factors. Indeed, when I present these results verbally, some immediately conclude that racial differences were due to white persons having superior education before I manage to finish the sentence with “and there were no differences in educational attainment between races”. For this reason, an important aspect of this study has been presenting the entire set of findings in context, and biases such as assumptions about alcohol, smoking and education being challenged. Authors represented all race groups reported in the study, the two lead authors being Black and Asian and the senior author being White. Patients of all races and ethnicities from the UK MS society were welcomed to discuss the conduct of this study, including people identifying as White, to ensure the study did not prejudice against any group.

Finally, a qualitative follow-up study is ongoing, which interviews participants from racially minoritized groups about their experiences with seeking healthcare, such that their narrative is presented without preformulated hypotheses.

*Ethical permits: Diarienummer 2017/1378-31 and 2019-02819 were approved for studies 1, 2, 3, 4. Study 5 ethical permits: Research Ethics Committee ref: 19/WA/0157 (University College London)*
5 Results

**Study 1: Association between early treatment of multiple sclerosis and patient-reported outcomes in Sweden**

There were 690–780 patients with relapsing MS propensity-matched for early treatment, and 2648 patients in the unmatched cohort, used for outcomes analyses. We demonstrated the benefit of early treatment, which is well established for EDSS as an outcome, also extends to patient-reported symptoms. Each year of delay in treatment (between 0–4 years from onset) was associated with a 17% (95%CI 8, 26%) higher burden of physical symptoms and 8% (95%CI 1, 15%) higher burden of psychological symptoms. Overall quality of life appeared unchanged.

**Study 2: Association between clinic-level quality of care and patient-level outcomes in Sweden**

We see confirmation that early treatment, as well as a longer duration of treatment, is associated with more favourable clinical (n=4802) and patient-reported (n=4215) outcomes, among people with relapse-onset MS. Encouragingly, other components of care such as visit frequency and MRI frequency appear to be beneficial for physical outcomes such as EDSS [beta estimate: -0.2 (95%CI -0.36, -0.03) per visit per patient-year; -0.58 (95%CI -0.83, -0.34) per MRI per patient-year] and MSIS-29 physical symptom subscale [-19%(95%CI -30,-8%) per visit per patient-year; -35%(95%CI -49,-19%) per MRI per patient-year], though this only applies to the relapse-onset cohort. The associations persisted after adjusting for individual patient treatment parameters. People with progressive-onset MS did not appear to derive any clinical (n=352) or symptomatic (n=205) benefit from any of the QoC measures.

**Study 3: Association between premorbid sociodemographic status and MS outcomes in Sweden**

Among 4195 working-age people with relapse-onset MS, higher premorbid educational attainment and income levels were associated less disability [EDSS –
0.16 (95% CI -0.20, -0.12) per income quartile; -0.47 (95% CI -0.59, -0.35) for tertiary vs primary educated, less physical symptoms [MSIS-29 physical subscore -14% (95% CI -18, -11%) per income quartile, -43% (95% CI -50, -35%) for tertiary vs primary educated], and less psychological symptoms [MSIS-29 psychological subscale: -12% (95% CI -16, -9%) per income quartile, 25% (95% CI -33, -17%) for tertiary vs primary educated]. Partnered people did not differ from single people on these measures, but marital separation prior to disease onset was associated with adverse outcomes. These associations were less pronounced in progressive-onset MS (n=362). Income was associated with EDSS [-0.30 (95% CI -0.48, -0.11) per income quartile] but not patient-reported symptoms, while tertiary education was associated with lower psychological symptoms [MSIS-29 psychological subscale -33% (95% CI -54, -1%)] compared to a primary school education. There were no statistically significant associations with marital status, although the direction of association mirrored that of the relapse-onset cohort.

**Study 4: Association between socioeconomic status and quality of multiple sclerosis care in Sweden**

While higher income was associated with marginally faster times from diagnosis to treatment (12.7 days faster per income quartile, 95% CI 25.2, 0.3), this difference is of negligible clinical significance. Likewise, higher educational attainment was associated with marginally higher frequency of clinic visits (incidence rate ratio for secondary vs primary school educated: 1.04, 95% CI 1.00, 1.08; similar but nonsignificant for tertiary vs primary school educated) and MRI scans (incidence rate ratio 1.07, 95% CI 1.01, 1.12 for secondary, 1.12 (95% CI 1.06, 1.19) for tertiary vs primary educated) during the first four years post diagnosis, after adjusting for median EDSS and ARR during this period.

**Study 5: Racial Disparities in Multiple Sclerosis Treatment and Outcomes in London, UK**

619 participants were included in the analysis, of which 79% were White, 8% Asian, 6% Black, 5% Mixed and 2% Other. Compared to White participants, both Black and Asian participants had greater disability [EDSS +1.38 (95% CI 0.83, 1.92) for Black participants, +0.68 (95% CI 0.20, 1.17) for Asian participants]. Black
participants experienced longer delays from MS onset to first DMT [51% longer (95%CI 21-92%)] and spent a lower proportion of their disease time on treatment [48% compared to White participants (95%CI 30-82%)]. These disparities were not explained by differences in educational attainment.
6 Discussion

**Study 1: Association between early treatment of multiple sclerosis and patient-reported outcomes in Sweden**

Study 1 demonstrates that early treatment, a quality indicator well-established to affect clinical outcomes (such as EDSS), is also effective in improving patient-reported symptoms of MS. This association was not self-evident. While MS is a progressive disease on clinical measures of outcome (such as EDSS and radiological measures), this is not so when quality of life is the outcome. Thus, it is not certain that interventions that affect disability will have a comparable effect on quality of life, and vice versa – this was demonstrated by the effectiveness of early DMT in mitigating disability and patient-reported physical symptoms, but lack of effectiveness in modifying overall health-related quality of life. Nonetheless, this study provides important evidence for early treatment being of tangible benefit to patients. Further studies pertaining to the effect of early treatment on other patient-relevant outcomes, such as income, work disability, cognition, or fatigue, may also be of interest to patients and their families.

**Study 2: Association between clinic-level quality of care and patient-level outcomes in Sweden**

Study 2 was the first to demonstrate an association between more frequent neurology visits and MRI scans and more favourable clinical and patient-reported outcomes in relapse-onset MS. These indicators already feature in many consensus-based guidelines, but have hitherto lacked evidence to justify them. Conversely, we see no association between QoC indicators and outcome in progressive onset disease. This does not mean that visits and MRIs have no benefit at all to this group; rather, it indicates that the frequency of these encounters may not be relevant to outcome. Importantly, the indicators do not capture potentially beneficial activity outside of the neurology visit such as rehabilitation or nursing care, nor does it capture differential effects in patients with new focal MRI activity vs no new focal MRI activity – this stratification was not possible due to lack of data, however, it would be
conceivable that treatment-eligible patients with focal inflammation on MRI may have a similar benefit to those with relapse-onset disease.

There are two main points of consideration with interpreting these results. First, we cannot be certain whether quality metrics in this study reflect actual care or clinicians’ data entry proficiency. One interpretation of our study may be that patient outcome is associated with the average willingness or ability of neurologists at each clinic to enter data on the Swedish MS registry. This is an inherent limitation of the data. Indeed, the quality metric of “baseline patient data completeness” had a small but statistically significant association with outcome in the relapsing MS cohort. More problematic is that those clinicians who were not entering visits were thereby not entering outcome data, precluding the ability to perform meaningful time-to-event analyses (which were originally planned), thus longitudinal mixed effects models were used, which are less dependent on temporal resolution of outcomes – including for PROMs that were not dependent on clinician data entry. Second, the lack of causal methodology does not permit us to draw conclusions about cause and effect. While offering visits, MRI scans, treatment and good record keeping may contribute to improved outcomes, it may also be a surrogate indicator for other explanatory variables such as levels of clinician interest in the disease, clinic staffing and expertise, or levels of healthcare engagement of the patient population.

**Study 3: Association between premorbid sociodemographic status and MS outcomes in Sweden**

Study 3 demonstrated striking associations between socioeconomic status and future MS severity, even adjusted for individual treatment exposures. While previous studies of socioeconomic status and MS severity (not all in UHC contexts) have similar findings, all suffered from potential reverse causation due to exposures being measured at or after diagnosis. We also found marital status was linked to MS outcomes, which has hitherto been unexplored. The effect sizes for these associations were greater than that of DMT exposure in the relapsing cohort. Importantly, these associations were also seen in the progressive-onset cohort.

The mechanisms underlying this is an open question. Social determinants of health are well studied in diseases attributed to lifestyle. Socioeconomic
deprivation and social isolation are associated with food insecurity, lack of access to a nutritious diet, substance misuse, decreased opportunity for physical activity, decreased opportunity for health-seeking, and increased stress, all of which are well established risk factors for developing for metabolic syndrome, cardiovascular disease, and cancer\textsuperscript{91,92,149,150}. However, socioeconomic status is not clearly associated with risk of developing MS, with epidemiological studies producing mixed results\textsuperscript{144,151,152}. An important next step is to determine whether socioeconomic status reflects a modifiable target for disease modification, such as systematic differences in diet\textsuperscript{153}, exercise\textsuperscript{154}, lifestyle\textsuperscript{155,156} or stress\textsuperscript{157} (despite paucity of high-level evidence for such targets affecting clinical outcomes\textsuperscript{155,158}). If the mechanism is demonstrated to be modifiable, this opens an avenue of disease modification for progressive-onset MS that presently has limited treatment options.

**Study 4: Association between socioeconomic status and quality of multiple sclerosis care in Sweden**

Study 4 demonstrates that one explanation for the link between higher socioeconomic status and better outcomes may be through higher QoC. As discussed in the literature review, this is in line with existing studies from UHC contexts that demonstrate overall higher use of specialist services among socioeconomically advantaged people, after adjustment for indication\textsuperscript{159,160}. The present study was the first to explore this within MS care. The magnitude of these differences in care, however, are minimal. They would be insufficient to explain the socioeconomic outcome disparities demonstrated in study 3. Putting studies 3 and 4 together, those who suffer greater socioeconomic deprivation appear to be in greater need of care given their poorer prognosis, thus the care is not distributed according to need. This introduces a conceptual distinction between *equity* – care according to need – rather than *equality* – equal care for all – as a goal for care provision. This distinction is discussed in detail in Part 7: Points of Perspective.

**Study 5: Racial Disparities in Multiple Sclerosis Treatment and Outcomes**

Study 5 highlights significant racial disparities in MS treatment and outcomes. While ample studies from user-pays contexts have demonstrated similar
disparities, this is the first study to highlight race inequality in MS care in a UHC context. This indicates that free healthcare is necessary but not sufficient for health equity. Future studies should be directed to understanding what other aspects of healthcare need to be addressed for equitable care. Such aspects may include patient perceptions of treatment, cultural safety of healthcare settings, or systemic biases.

Due to selection bias, the extent of racial disparities may not be captured in this cohort. It is conceivable that those agreeing to study enrolment are more able-bodied, are affluent enough to live proximally to the clinic, and have more positive attitudes towards healthcare encounters or medical research. The racial representation of the cohort is not representative of Greater London, which has a 53.8% White, 20.7% Asian and 13.5% Black population\(^{61}\) (compared to 79.2%, 7.8% and 6.1% in the study population respectively). This may conceal the true spectrum of disability and treatment experienced by people living with MS in London, and is problem inherent to the study design.

Though income data was collected as part of the study, it was not included as a model covariate for two reasons. First, not all participants earned a salary. Limiting analysis to only those with active income would be unfeasible due to lack of power. Second, even if the study were sufficiently powered and income were to dilute the association between race and adverse outcomes, the interpretation is ambiguous. If income is interpreted as a mediator, this partly externalises the blame for poorer outcomes to patients’ earning capacity (or discriminatory hiring or renumeration practices) rather than racial disparity. If income is interpreted as a collider (i.e., that income is a downstream result of both race and disability/treatment), this should not be included as a model covariate. The cross-sectional nature of the data does not permit distinction between the two.
7 Conclusions

Early treatment start is the cornerstone of improving outcomes for people with relapsing MS. In addition, other care factors appear to be beneficial in this group, but not for people with progressive-onset disease.

In Sweden, higher socioeconomic status is associated with better QoC to a small extent, but does not account for the large disparities in disease severity. The same socioeconomic disparities are also demonstrated in a UK cohort. In addition, racial minoritisation is associated with both poorer QoC and poorer outcomes in the UK. The findings highlight the importance of considering social determinants in the management and treatment of MS within UHC systems.

The interplay between sociodemographic factors and health outcomes is complex, emphasising that while UHC aims to equalise access to care, individual socioeconomic factors continue to influence healthcare and health outcomes significantly.
8 Points of perspective

8.1 Quality of care is remarkably high in Sweden.

Despite some variability between clinics, overall quality of MS care is extremely high in Sweden and differences across socioeconomic strata are minimal, indicating a highly functioning healthcare system. These relatively small associations between QoC and outcome cannot be extrapolated to other contexts due to boundary effects. For example, QoC metrics as measured in the UK regarding time to treatment – the most evidence-based quality indicator – do not overlap with Swedish metrics. The determinants of outcome in low- and middle-income countries are even less represented in these studies, as the effect of comorbid disease, socioeconomic deprivation, education and employment opportunity \(^{92}\), as well as access to primary healthcare and disability support (social, financial, medical and infrastructural) will likely outweigh any effect of the studied QoC indicators.

8.2 Patient-reported outcomes matter.

Few patients know, or care about, their EDSS score. Of the thousands of patients I have examined at the Royal Melbourne Hospital MS Centre and the Queen Square MS Centre, less than 5 have asked about their score. But all of them care about their function and quality of life, which have vastly different determinants outside of disability scores depending on their vocation, living circumstances, age, and aspirations \(^{135,138,162}\). For example, that pain is not relevant to EDSS leads to large discrepancies between clinical and patient-reported outcome measures. This discrepancy was demonstrated in Study 1, where interventions associated with clinically meaningful differences in clinical disability did not translate to any differences in overall quality of life. There are advantages of PROMs as an outcome measure over clinical measures, including a higher temporal frequency of measurement that does not depend on clinicians or clinic visits, as well as being a direct measure of patient experiences. The supposed disadvantages of PROMs – subjectivity and discrepancy from clinician assessment – are actually the entire point. The main disadvantage of PROMS is an overwhelming number of tools available and under development \(^{163-165}\) (with 405 PROs in MS identified in one study\(^{165}\)), some of which are highly disease- and
symptom-specific (such as the Modified Fatigue Impact Scale for measuring MS-related fatigue), and others generalisable across neurological diseases (such as the NeuroQoL instrument\textsuperscript{166}) or health states (such as the Work Productivity and Activity Impairment instrument\textsuperscript{167} or EQ5D instruments). There is lack of consensus regarding which domains should routinely be measured, using which tool, which hinders uptake and acceptance among the scientific community as a relevant outcome measure\textsuperscript{165}. Future studies to address this issue, including consultation with patient and carer advocacy groups, will help standardise PROM measurement in clinical trial or registry data collection and increase their use in outcomes research and quality benchmarking.

8.3 The association between education and MS outcomes is an opportunity for future research in disease biology.

A question that arises from study 3 is the mechanism by which premorbid sociodemographic status might influence disease outcome. Notably, sociodemographic status seems to be associated with the severity of progressive-onset MS—a subtype generally unaffected by DMTs or quality of MS care. This raises a critical question: Is the impact of sociodemographic status on MS outcomes modifiable through intervention? For instance, if the influence of higher sociodemographic status operates through the optimisation of comorbidities, behavioural/lifestyle factors, or ecological exposures post-diagnosis, then harnessing these intermediary factors could allow personalised disease modification. Conversely, if the influence of sociodemographic status is established prior to disease onset and remains unmodifiable thereafter, its utility may be confined to serving as a prognostic indicator. One possible neurobiological explanation for education and vocational functioning being linked with MS outcomes is that it may correlate with greater structural or functional brain reserve\textsuperscript{15,168,169}, which buffers against clinically manifest neurological injury. Future studies may investigate whether neural correlates of educational attainment, such as differences in regional brain volumes, can be identified in MS-affected brains.
There is not one universal “universal healthcare”.

There is a subtle but important distinction between a UHC paradigm that strives for equality vs equity. Both promote fairness, but equity achieves this by treating people differently based on their need.

Figure 2: Distinction between Equality and Equity

In a healthcare context, equality aims to provide equal care for all, regardless of individual circumstances such as ability to pay (akin to the concept of horizontal equity, or equal care for equal need). Equity aims to achieve the equal outcomes, which may require different care depending on the needs of individuals (akin to vertical equity, or unequal care for unequal needs\textsuperscript{170,171} – this is also termed proportionate universalism\textsuperscript{91,123}). An example of equality is providing healthcare in a standard language, in a standardised format, which guarantees the same service for all recipients across the population. Equitable healthcare may instead provide healthcare in different languages and formats for individuals with different needs. An example of this is the “purple truck” dialysis service in central Australia\textsuperscript{172}, where a roaming dialysis van visits remote Aboriginal communities on a semi-flexible schedule. Users do not adhere to a dialysis schedule, but access this service wherever and whenever they choose. In-person interpreters are available for all major regional languages. This format strives to help “close the
gap”, or equalise, Aboriginal vs Nonaboriginal mortality due to end stage renal failure (a health outcome rather than a care utilisation indicator), by ensuring that indigenous Australians who do not speak English, or have a nomadic or itinerant way of living, are able to dialyse as effectively as English-speaking, fixed-residence people\textsuperscript{172,173}.

NHS England also strives to achieve health equity by proactively measuring and correcting disparities in outcome. Equity is an explicit goal of the NHS\textsuperscript{174,175}, and is defined as “Where health outcomes do not differ according to personal characteristics such as ethnicity, geographical location or socioeconomic status\textsuperscript{176}”. An example of an NHS equity policy is maternity care. Mothers from BAME backgrounds experience two- to fivefold higher perinatal mortality compared to White mothers, while mothers living in areas with the highest deprivation indices have a twofold increase in mortality compared to the least deprived. Continuity of care is an evidence-based quality measure that mitigates adverse maternal and neonatal outcomes. The national quality target for continuity of carer is a modest $20-50$\textsuperscript{174,177}. The target for women of BAME background or high deprivation indices is $75\%$\textsuperscript{174,176,177}. Another equity initiative is the establishment of the NHS Race and Health Observatory, whose function is to identify, address, and reduce racial and ethnic health disparities in NHS England through research, developing policy recommendations, promoting best practices, and stakeholder engagement\textsuperscript{186}.

Sweden provides UHC that all residents can access at a low price ceiling. Based on the philosophy that all individuals have equal value, the explicit goal of the Swedish healthcare system is equal care for the entire population; moreover, that care should be of high quality and accessible.

According to Swedish Health Care Act (Swedish: Hälso- och sjukvårdslagen (1982:763)), “The objective of health care is good health and care on equal terms for the entire population.” (Swedish: “2 § Målet för hälso- och sjukvården är en god hälsa och en vård på lika villkor för hela befolkningen”).

However, the Ministry of Health and Social Welfare (Swedish: Socialstyrelsen), in their publication “National indicators for good care – healthcare overarching indicators, indicators in the Ministry of Health and Social Welfare national guidelines\textsuperscript{178a}” (Swedish: “Nationella indikatorer för God vård – Hälso- och sjukvårdsövergripande indikatorer – Indikatorer i Socialstyrelsens nationella riktlinjer”, article number 2009–11–5), explains that: “Equal care means that
reception, care, and treatment should be offered on equal terms to all, regardless of personal characteristics, place of residence, age, gender, disability, education, social status, ethnic or religious affiliation or sexual orientation. As health is not equally distributed, health care that strives to achieve good health and equal treatment for the whole population should prioritize those with the greatest needs.” (Swedish: “Jämlik vård innebär att bemötande, vård och behandling ska erbjudas på lika villkor till alla oavsett bland annat personliga egenskaper, bostadsort, ålder, kön, funktionshinder, utbildning, social ställning, etnisk eller religiös tillhörighet eller sexuell läggning. Eftersom hälsan inte är jämlikt fördelad bör en sjukvård som strävar efter att uppnå en god hälsa och en vård på lika villkor för hela befolkningen prioritera de som har störst behov.”) The dissonance in this statement highlights the distinction between equality (sentence 1) and equity (sentence 2). In the same publication, 20 national indicators of good care are stipulated. The equity principle is not captured in these indicators – instead, these reflect population-level outcome measures, such as preventable deaths, preventable admissions and suicides, without stratification by risk factors or social determinants. By optimising these indicators on an aggregated population level, a disparity that affects a minority group may not be captured unless the distribution of these indicators is monitored in a disaggregated way. In a similar vein, the Swedish national MS guidelines stipulate goals for equal care as well as equal outcomes. However, as this thesis has demonstrated, it is not true that equal outcomes can be achieved through equal care (or that unequal outcomes are resultant from unequal care). The differences in MS outcomes between high- and low-income persons cannot be equalised by shortening diagnosis-to-treatment times of the latter by 25 days. Would a more nuanced, stratified and equity-driven approach to quality indicators help address health inequalities?

We do not know the effectiveness of “equity” interventions such as those spearheaded by NHS England, let alone the relative merits of an equity- vs equality-based philosophy of healthcare. Moreover, if we are to believe extensive research regarding social determinants of health, the role of healthcare is marginal in comparison to the social determinants, or “causes of causes”, of poor health91\textsuperscript{12,3,49}. Thus, equity in healthcare may be insufficient to compensate for the disadvantage imparted by, for example, socioeconomic deprivation or race. A more holistic approach may instead involve equalisation of these social determinants, which lies in the domain of politics and policy rather than healthcare – this concept is exemplified by Nordic countries, which consistently
have among the world’s highest levels of social capital and highest measures of life satisfaction\textsuperscript{179}. There are no randomised controlled trials of health equity interventions. However, numerous frameworks have been suggested for such trials\textsuperscript{180,181}.

**Table 1**: Relationship between causes and outcomes of the five main causes of death and disability in the UK

<table>
<thead>
<tr>
<th>Distal risk factors (‘Causes of the causes’)</th>
<th>Intermediate risk factors</th>
<th>Proximal risk factors</th>
<th>Outcomes (5 main causes of death and disability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socioeconomic factors</td>
<td>Tobacco</td>
<td>High blood pressure</td>
<td>Heart disease</td>
</tr>
<tr>
<td>Genetics</td>
<td>Alcohol</td>
<td>High cholesterol</td>
<td>Cancer</td>
</tr>
<tr>
<td>Epigenetics</td>
<td>Unhealthy diet</td>
<td>High glucose</td>
<td>Chronic lung diseases</td>
</tr>
<tr>
<td>Exposures in the womb and early life</td>
<td>Physical inactivity</td>
<td>Obesity</td>
<td>Diabetes</td>
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<tr>
<td></td>
<td>Air pollution</td>
<td></td>
<td>Mental health disorders</td>
</tr>
</tbody>
</table>

Commissioned report: *Ethnic disparities in the major causes of mortality and their risk factors in the UK – submission to the Commission on Race and Ethnic Disparities*. 28 April 2021. Authors: Raghib Ali, Avirup Chowdhury, Nita Forouhi, Nick Wareham. MRC Epidemiology Unit, University of Cambridge.\textsuperscript{182}

### 8.5 Race remains a highly sensitive issue for clinical research.

Many clinicians are uncomfortable with studying race-based health outcomes, not least due to the perceived possibility of uncovering of racist practices. When such studies are conducted, tendency for medical gaslighting (such as implicating failure to attend medical appointments, poor health behaviours or poor medication compliance) fails to address the problem of breakdown in trust, shared goal-setting and shared management. That structural racism exists is not putting blame on individual clinicians but acknowledging the existence of systematic and complex barriers to health equity that, much like equalising initiatives, may require differences in approach based on individual need. While not by design, the default healthcare model in any society will naturally suit the dominant culture, while culturally safe healthcare for ethnic minorities is not “standard practice”. The purpose of this and follow-on studies is to identify opportunities for improvement.

Many clinicians correctly believe they provide equal care to all race groups. That the same care can be received differently by different patients is not just a
result of differences in cultural safety of the “standard care” paradigm\textsuperscript{183}, but also a complex legacy of inherited traumas, personal or vicarious prior experiences of discrimination, vicarious mistrust/iatrophobia that leads to systematic differences in patient perception of care and clinician–patient relationships\textsuperscript{184–187}.

NHS England has comprehensive strategic plan for overcoming such barriers, including equalising ethnic representation at all levels of medical care. There are no black neurologists at Queen Square MS Centre, despite a large cohort of black patients. Representation, especially at highest levels of management, is a crucial component of equalising racial disparities in health care and outcomes. Furthermore, this can only be achieved with conscious intention, by recruiting, retaining, promoting, and increasing the quality of life of BAME staff at all levels – another recommendation of NHS England’s Race and Health Observatory report\textsuperscript{116}. Finally, the report emphasises genuine community outreach. Existing MS society patient and public involvement (PPI) programs do not explicitly target racially diverse communities. Intentional inclusivity in patient advocacy is a necessary measure to ensure diverse patient voices are being amplified.

In line with this ambition, and as a follow-up to Study 5, ethical approval has been obtained for a qualitative study of the healthcare experiences of the Black participants in the PITMS study cohort. Semi-structured interviews will explore experiences of diagnosis, treatment, and healthcare interactions, with thematic analysis to generate hypotheses for future quantitative studies.
"The function of freedom is to free someone else."

Toni Morrison
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