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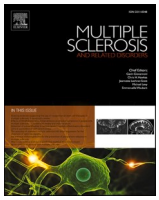

Original article

# Evaluating the feasibility of a real world pharmacovigilance study (OPTIMISE:MS)

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ABSTRACT

*Background:* Clinical trial populations do not fully reflect routine practice. The power of routinely collected data to inform clinical practice is increasingly recognised.
*Methods:* The OPTIMISE:MS pharmacovigilance study is a prospective, pragmatic observational study, conducted across 13 UK MS centres. Data were collected at the time of routine clinical visits. The first participant was recruited on 24th May 2019; data were extracted on 11th November 2021.
*Results:* 2112 participants were included (median age 44.0 years; 1570 (72%) female; 1981 (94%) relapsing-remitting MS). 639 (30%) were untreated at study entry, 205 (10%) taking interferon beta/copaxone, 1004 (47%) second/third generation DMT first line and 264 (13%) had escalated from a platform DMT. 342 clinical events were reported, of which 108 infections. There was an increased risk of adverse events in people taking second/third generation DMT (RR 3.45, 95%CI 1.57-7.60, $p<0.01$ vs no DMT). Unadjusted Poisson regression demonstrated increased incident adverse events in people taking natalizumab (IRR 5.28, 95%CI 1.41-19.74, $p<0.05$), ocrelizumab (IRR 3.24, 95%CI 1.22-8.62, $p<0.05$), and GA biosimilar (Brabio) (IRR 4.89, 95%CI 1.31-18.21, $p<0.05$) vs no DMT.

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*Conclusions:* Routinely collected healthcare data can be used to evaluate DMT safety in people with MS. These data highlight the potential of pragmatic studies to guide understanding of risks and benefits associated with DMT.

## 1. Introduction

There has been a rapid expansion in the range of disease modifying therapies (DMT) used to treat multiple sclerosis (MS) over the past 10 years (De Angelis, John and Brownlee, 2018). Results from clinical trials are used to guide discussions around treatment-associated risks and benefits, yet it is increasingly recognised that clinical trial populations do not fully reflect the range of people with MS treated in routine clinical practice (Trojano et al., 2017). Many clinical trials have age restrictions and routinely exclude people with significant co-morbidities (Jalusic et al., 2021), and studies are powered to detect disease activity related endpoints, rather than rare adverse events.

Unanswered questions remain around the risks of DMTs in real world populations and optimal treatment sequencing to balance risks and benefits, which cannot be answered using traditional randomised control trial (RCT) design. Whilst phase 4 observational studies have been used to provide data addressing these questions, the power of routinely collected clinical data to help inform clinical practice is increasingly being recognised. The use of data from the full spectrum of people with MS, including those from a range of backgrounds and ages and with a variety of comorbidities has the ability to improve our understanding of the risks and benefits associated with DMT use in clinical populations. However, real world data is confounded in its own way – participants in observational studies are not prospectively randomised, treatment strategies are not selected at random but related to likely prognosis, and there is substantial variation in practice across a single country (Cameron et al., 2019).

The most serious risks common to all of the immunomodulatory and immunosuppressive MS treatments are infection and malignancy, with severe opportunistic infections a particular concern. Progressive multifocal leukoencephalopathy (PML) risk limits the long-term use of natalizumab (D'Amico et al., 2016). There are safety signals from clinical trials and early clinical experience suggesting both lymphopenia and increased overall and opportunistic infection rates with newer MS therapies (Khatri et al., 2015, Fitzgerald, 2015, Oh and O'Connor, 2015). Anti-CD20 therapies are associated with greater severity of COVID-19 (Simpson-Yap et al., 2021). Any increased risk of cancer is also not adequately captured during the timespan of a clinical trial (Grytten et al., 2021).

The OPTIMISE:MS pharmacovigilance study is a prospective, pragmatic observational study, conducted across 13 UK MS centres. This study aims to address the need for real world pharmacovigilance in MS by recruiting 4000 people living with MS, and following their clinical outcomes for up to 5 years (Dobson et al., 2021). It provides data on outcomes in specialist MS centres, where most UK MS care is provided. We present the initial data from the first 2112 people with MS enrolled in the study, along with drug exposures captured and early signals of adverse events.

## 2. Methods

### 2.1. Patient cohort

Study design, recruitment and the core dataset have previously been described in detail (Dobson et al., 2021). Briefly, eligible participants are those people diagnosed with MS who are eligible to receive DMT according to NHS guidelines (NHS England or Scotland). This includes people with MS taking DMT, as well as those starting, potentially eligible to start but not receiving DMT, or switching DMT with either relapsing-remitting or progressive MS. Participants for this analysis were recruited from 13 sites across the UK. The first participant was recruited on 24th May 2019. There were subsequent interruptions to recruitment during 2020-21 as a result of COVID-19.

Clinical data, clinical histories, laboratory and paraclinical tests results are collected in a harmonized fashion across sites at the time of routine clinical visits or follow up via entry into a study-specific database (OPTIMISE) by treating clinicians or other members of the MS team. Where routine clinical appointments were carried out virtually, these data were also included. The complete dataset collected is described in detail elsewhere (Dobson et al., 2021). Core baseline data includes MS-specific measures including Expanded Disability Status Scale (EDSS), relapses within the 2 years prior to study entry, current and previous DMT, and MRI results where available. Additional data including comorbidities at the time of study entry, concomitant medications, prior malignancies and opportunistic infections and laboratory measures including lymphocyte count and liver function are also collected. Follow up data, entered on at least an annual basis, includes current DMT and date of switch where relevant, EDSS, relapses, serious adverse events, and concomitant medications. Where infusion reactions are of sufficient severity to count as a serious adverse event (i.e. requiring admission) they are captured.

Patient-level data is entered into a study-specific database on at least an annual basis, and at the time of direct follow up if sooner. The database contains pre-specified fields for all new and follow up data, which sites complete using clinical records as source data. New diagnoses and adverse events are MedDRA coded at the time of entry. Every data entry is time stamped according to both date of data entry and data of data collection to allow for audit and identification of substantially retrospective data entry. Data are transferred electronically, on at least a monthly basis, to the central site for central storage and analysis. All data is pseudonymised at the time of transfer. Identifiable data is retained at sites within the locally held databases to allow patient follow up, and separately to all other data at the coordinating site for the purposes of electronic health care data linkage at a later date.

The aggregated data from participating sites analysed in this paper was extracted from the central OPTIMISE:MS database on 11 November 2021. All participants enrolled in the study with at least one recorded visit containing baseline data were included in this analysis.

### 2.2. Statistical analysis

Standard descriptive statistics are used to describe the study population. Control groups are classified as those taking either (1) no disease modifying therapies (DMT), and (2) those on platform (first generation) injectable DMT - glatiramer acetate and interferon Beta (GA-IFN). Poisson regression was used to evaluate rates of (1) any events and (2) non-relapse adverse events in subjects receiving any second or third generation DMT in comparison to those receiving GA-IFN or no treatment. A mixed model with fixed treatment effects and random intercepts was used. Unadjusted analyses were first performed, prior to adjustment for site of enrolment. Further adjustments for age, disease duration and gender were not performed due to power concerns, however these are planned in the final analysis. A second analysis was then performed according to individual DMT.

Drug-event signals were analysed by identifying specific DMTs associated with disproportionate numbers of events relative to the overall study population. For each drug-event combination, a longitudinal Reporting Odds Ratio (ROR) was derived, comparing the odds of the event occurring in a drug-exposed patient-month with the odds in an unexposed patient-month; disproportionality signals were triggered

**Table 1**
Baseline demographics of the 2112 participants.

| | All patients | No DMT | 1st generation DMT (IFN-β or GA) | Patients receiving 2nd generation DMT (no prior 1st generation DMT) | Patients receiving 2nd generation DMT (with prior 1st generation DMT) |
|---|---|---|---|---|---|
| **Patients enrolled in study with at least one recorded visit, n (%)** | 2112 (100%) | 639 (30%) | 205 (10%) | 1004 (47%) | 264 (13%) |
| **Sex, n (%)** | | | | | |
| Male | 587 (28%) | 186 (29%) | 45 (22%) | 295 (29%) | 61 (23%) |
| Female | 1520 (72%) | 452 (71%) | 160 (78%) | 707 (70%) | 201 (76%) |
| **Age (years)** | | | | | |
| Mean (SD) | 44.0 (11.07) | 44.3 (11.45) | 48.5 (10.68) | 42.6 (10.98) | 44.9 (9.60) |
| Median (range) | 44.0 (18-82) | 44.4 (18-82) | 48.7 (23-73) | 42.4 (18-75) | 44.7 (18-71) |
| **Ethnicity, n (%)** | | | | | |
| White | 1610 (76%) | 514 (80%) | 165 (80%) | 714 (71%) | 217 (82%) |
| Asian | 113 (5%) | 26 (4%) | 6 (3%) | 70 (7%) | 11 (4%) |
| Black | 84 (4%) | 17 (3%) | 0 (0%) | 58 (6%) | 9 (3%) |
| Mixed / Multiple ethnic groups | 62 (3%) | 19 (3%) | 5 (2%) | 31 (3%) | 7 (3%) |
| Other ethnic groups | 53 (3%) | 12 (2%) | 4 (2%) | 29 (3%) | 8 (3%) |
| Unknown | 190 (9%) | 51 (8%) | 25 (12%) | 102 (10%) | 12 (5%) |
| **Primary MS diagnosis, n (%)** | | | | | |
| Unknown | 12 (1%) | 6 (1%) | 2 (1%) | 3 (<1%) | 1 (<1%) |
| RRMS | 1990 (94%) | 566 (89%) | 197 (96%) | 965 (96%) | 262 (99%) |
| PPMS | 63 (3%) | 42 (7%) | 1 (<1%) | 20 (2%) | 0 (0%) |
| SPMS | 42 (2%) | 22 (3%) | 4 (2%) | 16 (2%) | 0 (0%) |
| **Time since diagnosis (years)** | | | | | |
| Mean (SD) | 8.5 (7.45) | 7.4 (7.61) | 10.6 (8.41) | 8.0 (7.10) | 11.7 (6.35) |
| Median (range) | 6.9 (0-47) | 5.5 (0-47) | 8.6 (0-43) | 6.0 (0-39) | 11.0 (0-32) |
| **Estimated EDSS, n (%)** | | | | | |
| <1 | 72 (6%) | 26 (11%) | 8 (6%) | 33 (5%) | 5 (3%) |
| 1 - 2.5 | 556 (44%) | 107 (44%) | 58 (42%) | 317 (45%) | 74 (41%) |
| 3 - 4.5 | 315 (25%) | 55 (22%) | 40 (29%) | 180 (25%) | 40 (22%) |
| 5 - 6.5 | 317 (25%) | 55 (22%) | 30 (22%) | 174 (24%) | 58 (32%) |
| >=7 | 15 (1%) | 2 (1%) | 1 (1%) | 8 (1%) | 4 (2%) |
| Median (range) | 3.0 (0-8.0) | 2.5 (0-7.5) | 3.0 (0-7.0) | 3.0 (0-8.0) | 3.0 (0-7.0) |

when the lower 95% confidence limit for the ROR exceeded 1. The ROR however can be volatile and liable to generate false positives when event counts are low. To address this, a minimum number of events was imposed so that extremely low counts were excluded from the analysis; additionally, the Bayesian Confidence Propagation Neural Network was used to shrink disproportionality estimates based on low event counts back towards the null hypothesis of no association. A chronological filter based on the LEOPARD methodology was then applied (Schuemie, 2011) in order to assess whether an adverse event occurred more often before or after the prescription of the treatment with which it appeared to be associated.

Signals were reported if the minimum number of events was observed, the lower 95% confidence limit for the Reporting Odds Ratio exceeded 1, the BCPNN False Discovery Rate was below 5% and the LEOPARD filter indicated that the data are consistent with an increase in the event rate after prescription of the drug.

Finally, a simple disproportionality analysis stratified by site for each signal was then performed. A Reporting Odds Ratio (ROR) was calculated within each site, and compared across sites in order to examine for bias driven by single sites.

All statistical analysis was performed using R version 4.0.3.

### 2.3. Ethical review

All participants provided written informed consent to take part in this study. This study has ethical approval (London City and East REC ref. 19/LO/0064).

**Table 2**
DMT exposure in patient-months by year.

| | 2019 | 2020 | 2021 | Total |
|---|---|---|---|---|
| Alemtuzumab (Lemtrada) | 266 | 1040 | 883 | **2189** |
| Cladribine (Mavenclad) | 145 | 480 | 565 | **1190** |
| Dimethyl fumarate (Tecfidera) | 375 | 1859 | 2130 | **4364** |
| Fingolimod (Gilenya) | 190 | 1142 | 1276 | **2608** |
| Glatiramer acetate (Copaxone) | 171 | 705 | 724 | **1600** |
| Glatiramer acetate biosimilar (Brabio) | 22 | 175 | 193 | **390** |
| Interferon beta-1a (Avonex) | 46 | 308 | 352 | **706** |
| Interferon beta-1a (Rebif) | 83 | 340 | 358 | **781** |
| Interferon beta-1b (Betaferon) | 4 | 28 | 38 | **70** |
| Natalizumab (Tysabri) | 644 | 3481 | 3975 | **8100** |
| Ocrelizumab (Ocrevus) | 661 | 2336 | 2544 | **5541** |
| Peginterferon beta-1a (Plegridy) | 21 | 127 | 164 | **312** |
| Rituximab (Mabthera, Truxima) | 5 | 25 | 20 | **50** |
| Teriflunomide (Aubagio) | 144 | 340 | 361 | **845** |

* Exposure to Alemtuzumab and Cladribine is considered to persist for 2 years after the final dose, or until a new DMT is initiated if this occurs within 2 years.

## 3. Results

Baseline demographics of the 2112 participants (mean age 44.0 years; median age 44.0 years, range 18-82 years old) are given in Table 1. 639 (30%) were untreated at the time of study entry, 205 (10%) were taking a GA-INT, 1004 (47%) were treated with second/third generation therapy first line and 264 (13%) had been escalated from a GA-IFN (Table 2). 1570 (72%) of the cohort were female, and 1981

**Table 3**
Clinical events in study population during follow up.

| Event type | Patients | % of study population | Events |
|---|---|---|---|
| Any Event | 238 | 11 | 342 |
| Any SAE* | 171 | 8 | 237 |
| New symptom | 18 | 1 | 20 |
| Relapse | 78 | 4 | 85 |
| Infection | 79 | 4 | 108 |
| UTI | 40 | 2 | 54 |
| Viral | 5 | <1 | 5 |
| Abscess | 0 | 0 | 0 |
| Bacterial | 13 | 1 | 15 |
| Sepsis | 0 | 0 | 0 |
| Sinusitis | 1 | <1 | 1 |
| Gastroenteritis | 1 | <1 | 1 |
| Other | 3 | <1 | 4 |
| (no classification recorded) | 27 | 1 | 28 |
| COVID | 37 | 2 | 37 |
| Suspected | 4 | <1 | 4 |
| Confirmed | 20 | 1 | 20 |
| Hospitalised | 2 | <1 | 2 |
| Ventilated | 3 | <1 | 3 |
| (no classification recorded) | 8 | <1 | 8 |
| Opportunistic Infection | 29 | 1 | 36 |
| Herpes Zoster | 9 | <1 | 9 |
| Varicella | 1 | <1 | 1 |
| Herpes Simplex | 0 | 0 | 0 |
| PML | 0 | 0 | 0 |
| Abscess | 1 | <1 | 1 |
| Other infection | 6 | <1 | 7 |
| (no classification recorded) | 15 | 1 | 18 |
| Malignancy or suspected ADR | 16 | 1 | 18 |
| Death | 3 | <1 | 3 |
| Other SAE | 27 | 1 | 35 |

* Throughout this report "SAE" refers to any event other than new symptoms or relapses.

**Table 4**
Demographic variables by SAE occurrence during follow up.

| | All patients | Did not experience SAE | Experienced SAE |
|---|---|---|---|
| **Patients enrolled in study with at least one recorded visit, n (%)** | 2112 (100%) | 1804 (85%) | 308 (15%) |
| **Sex, n (%)** | | | |
| Male | 587 (28%) | 509 (28%) | 78 (25%) |
| Female | 1520 (72%) | 1290 (72%) | 230 (75%) |
| **Age (years)** | | | |
| Mean (SD) | 44.0 (11.07) | 43.8 (11.0) | 45.2 (11.42) |
| Median (range) | 44.0 (18-82) | 43.6 (18-75) | 45.5 (18-82) |
| **Ethnicity, n (%)** | | | |
| White | 1610 (76%) | 1378 (76%) | 232 (75%) |
| Asian | 113 (5%) | 86 (5%) | 27 (9%) |
| Black | 84 (4%) | 74 (4%) | 10 (3%) |
| Mixed / Multiple ethnic groups | 62 (3%) | 53 (3%) | 9 (3%) |
| Other ethnic groups | 53 (3%) | 41 (2%) | 12 (4%) |
| Unknown | 190 (9%) | 172 (10%) | 18 (6%) |
| **Primary MS diagnosis, n (%)** | | | |
| RRMS | 1990 (94%) | 1701 (94%) | 289 (94%) |
| PPMS | 63 (3%) | 54 (3%) | 9 (3%) |
| SPMS | 42 (2%) | 34 (2%) | 8 (3%) |
| Unknown | 12 (1%) | 11 (1%) | 1 (<1%) |
| **Time since diagnosis (years)** | | | |
| Mean (SD) | 8.5 (7.45) | 8.2 (7.25) | 10.7 (8.2) |
| Median (range) | 6.9 (0-47) | 6.5 (0-47) | 9.0 (0-39) |

(94%) had a diagnosis of relapsing remitting MS. DMT exposure is given in Table 2. Participants were assumed to have ongoing exposure to alemtuzumab or cladribine for 2 years following the final dose, or until a new DMT was initiated, whichever occurred sooner.

### 3.1. Clinical events

342 clinical events were reported during follow up (Table 3). 85 (24.9%) of these were for a clinical relapse, and 20 (5.8%) were for new MS symptoms. A total of 108 infections were reported, of which half (54, 50.0%) were urinary tract infections. 37 cases of COVID-19 were reported in 37 participants. 5 of these participants were reported to have been hospitalised with COVID-19, with 3 ventilated, one of whom died.

36 opportunistic infections were reported in 29 participants. The most commonly specified of these was herpes zoster infection (9 reports). No herpes simplex or PML cases were reported. Details of those experiencing adverse events are given in Table 3. Those with adverse events had a significantly longer history of MS (p=0.006).

### 3.2. Risk of adverse events

An increased risk of adverse events (excluding MS relapses and symptom worsening) was seen in people taking second/third generation DMT compared to those on no DMT (rate ratio [RR] 3.45, 95% confidence interval [95%CI] 1.57-7.60, p<0.01); the increased risk persisted when incident events only were included (incidence rate ratio [IRR] 2.50, 95%CI 1.07-5.81). A similar increased risk was seen when second/third generation DMT were compared to GA-IFN (RR 2.64, 95%CI 1.06-6.61, p<0.05) (Table 4). People taking second/third generation DMT also had an increased rate of any adverse event (including MS relapse or symptom deterioration) compared to those on no DMT (RR 2.72, 95%CI 1.44-5.13, p<0.01), but not compared to those on GA-IFN (Table 4).

Unadjusted Poisson regression by DMT demonstrated an increased rate of incident adverse events (excluding relapses and new MS symptoms) in people taking natalizumab (incidence rate ratio [IRR] 5.28, 95% confidence interval [95%CI] 1.41-19.74, p<0.05), ocrelizumab (IRR 3.24, 95%CI 1.22-8.62, p<0.05), and glatiramer acetate biosimilar (Brabio) (IRR 4.89, 95%CI 1.31-18.21, p<0.05) compared to people on no DMT. This effect persisted for both natalizumab (RR 9.18, 95%CI 2.96-28.47, p<0.001) and ocrelizumab (RR 3.78, 95%CI 1.73-18.53, p<0.01) when recurrent events in the same patient were also considered.

Event rates and prescribing patterns were observed to differ by site (figure 1); in order to evaluate the potential impact of site-level confounding, recruitment site was included in the model as a confounding covariate in a sensitivity analysis. In this model significantly elevated event rates were only seen for natalizumab only (unadjusted RR 5.59, 95%CI 1.97-17.44, p<0.01; adjusted by site RR 5.42, 95%CI 1.66-17.66, p<0.01).

When all events (including relapses and new MS symptoms) were considered, people taking glatiramer acetate biosimilar (Brabio) showed a signal for an increased risk in the unadjusted analysis (incidence rate ratio for people taking Brabio vs. no DMT IRR 4.89, 95%CI 1.55-14.40, p<0.01; incidence rate ratio people taking Brabio vs. all other DMT IRR 3.64, 95%CI 1.22-10.89, p<0.05). However, this signal was lost when the regression model was adjusted by site. An increased rate of all events (including recurrent events) was seen in the unadjusted model for people taking natalizumab (RR 4.48, 95%CI 1.48-13.56, p<0.01), ocrelizumab (RR 2.90, 95%CI 1.32-6.37, p<0.01) and glatiramer acetate biosimilar (Brabio) (RR 3.57, 95%CI 1.19-10.67, p<0.05) compared to no DMT. There was no significant increase for any DMT in the model adjusted for site. It should be noted that the adjusted analyses may remain underpowered, particularly for less frequently used drugs, as some sites may not have recorded sufficient data to estimate the site-specific effects with sufficient precision.

In the drug-specific analysis, a number of infection-related signals

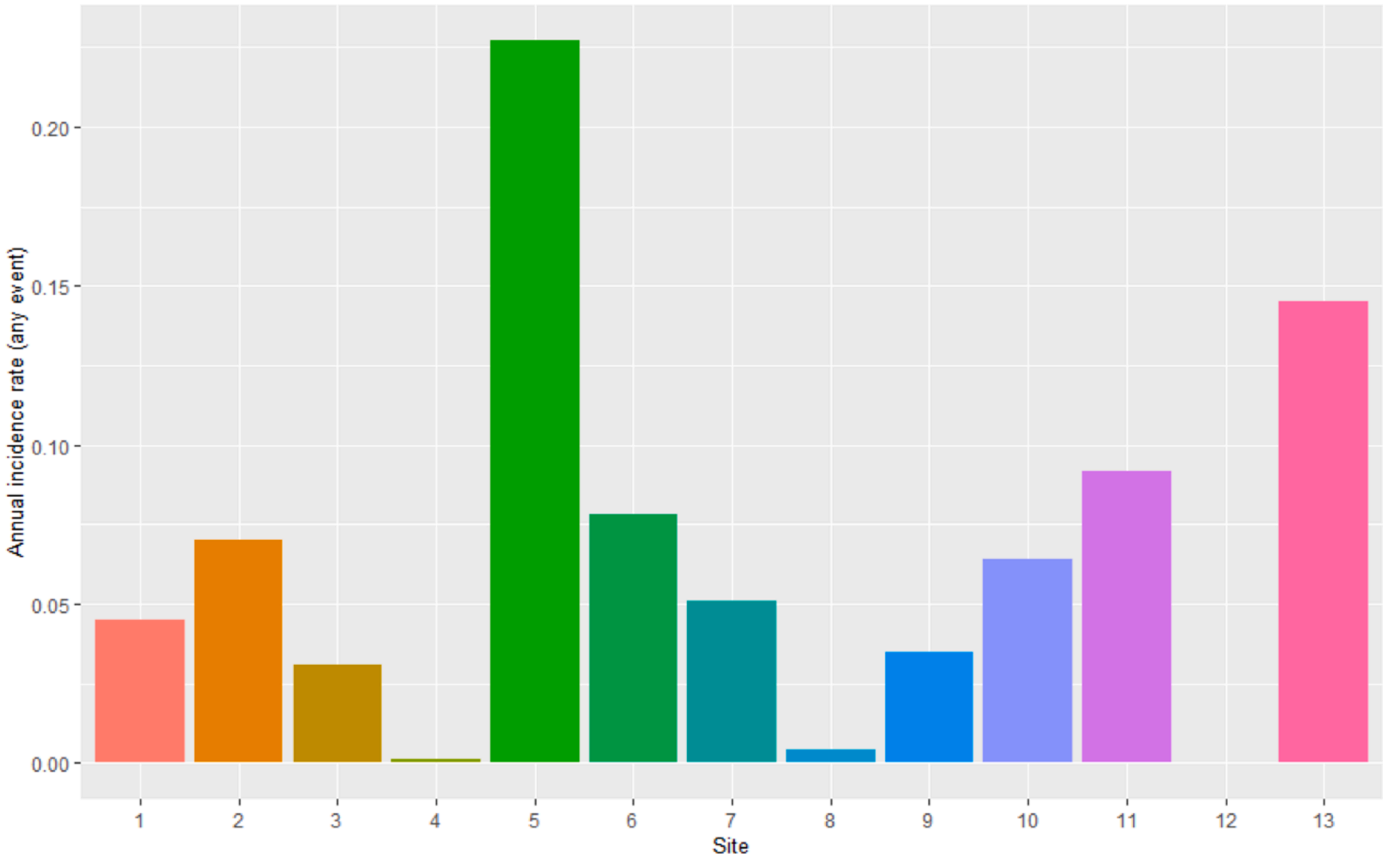


**Fig. 1.** Event incidence rate by site.

related to alemtuzumab and natalizumab use were seen (figure 2). Specific signals related to individual DMT are given in supplementary table 1. For all of the reported signals, the log ROR was greater than 0 (indicating a potential drug-event association) for at least one site, usually for several sites, and often significantly so (supplementary data).

## 4. Discussion

Here we demonstrate how routinely collected healthcare data can be used to evaluate the safety of DMT for people with MS. We have shown that it is possible to distinguish drug-related and disease-activity related risks. Whilst participant numbers and follow-up times in the data currently presented limit conclusions that can be drawn concerning rare serious adverse events, this early data highlights the potential of an inexpensive, pragmatic study such as OPTIMISE:MS to deliver information that can guide a better understanding of the risks and benefits associated with the treatment in real-world populations. Understanding the impact of adverse events on treatment decision, particularly treatment switching is an important next step. Whilst this was not possible given the limited follow up duration in the current analysis, we anticipate that this will be an important outcome from this study.

As expected, the population included in our study was both larger and more diverse than in typical clinical trials. With an age range of 18-82, and range of prior DMT exposures, this cohort better reflects current DMT use in tertiary MS clinics across the UK than the pivotal clinical trials. Although still early in the course of the study, this early review of the data from over 120,000 patient months of DMT exposure, already contributes to better understanding the real-world impact of DMT on people living with MS.

Differences in both event rates and prescribing practices at site level may well be linked; whilst at present this study does not have sufficient power to investigate this in detail, future analyses will be able to establish with more certainty the relationship(s) and interactions between DMT, adverse event rates and reporting practice. The increased number of both all and non-MS related adverse events associated with natalizumab was unexpected and the underlying reasons for this are uncertain. One possibility is that there is more accurate ascertainment of adverse events with natalizumab than with other DMT. Natalizumab is the DMT associated with most frequent healthcare contacts, with infusions required on a 4-6 weekly basis. In addition, because of the greater risks of serious infections than with other DMT, there is typically enhanced vigilance for both new MS symptom onset and for any symptoms that could be associated with infection in people receiving this medication. Similarly, detection of paucisymptomatic urinary tract infection in the course of alemtuzumab drug monitoring may have driven this drug-specific signal. In a similar way, the lack of autoimmune adverse events for the population taking alemtuzumab may at first appear surprising. However, it must be noted that with the current numbers of patients who started alemtuzumab during the study period, it is unlikely that sufficient relevant incident adverse events were recorded to reach the reporting threshold.

Our preliminary study report is not without weaknesses. First is the short follow up period, which limits the power to detect events. At present, we have insufficient follow up time and power in order to adequately assess the effect of treatment switching and concomitant medication use on the occurrence of adverse events. As the follow up period increases, we also plan to study the impact of both time on therapy and age at treatment initiation (and continuation) on risk of adverse events, however to do so at this stage would be premature. There is likely to be substantial confounding around DMT choice in this real-world observational study, with those people with more highly active disease, or a more favourable comorbidity profile being offered more highly effective therapy. However, as the long-term benefits of early, highly active DMT on disability outcomes becomes increasingly

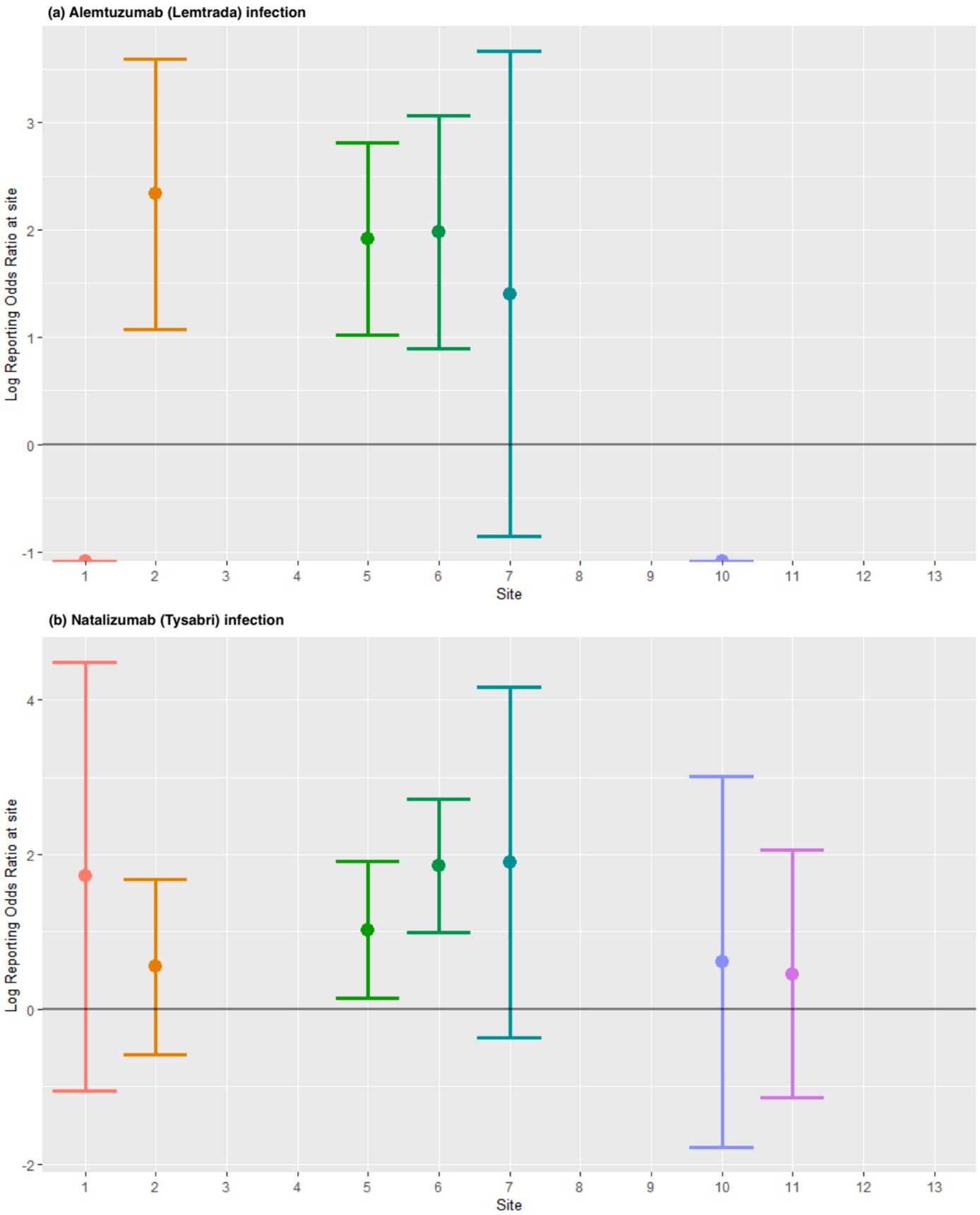


**Fig. 2.** Within-site Reporting Odds Ratios for signals on Level 3 List (a) Alemtuzumab (Lemtrada) infection (b) Natalizumab (Tysabri) infection (c) Natalizumab (Tysabri) any (d) Natalizumab (Tysabri) viral (e) Natalizumab (Tysabri) new MS symptom (f) GA Biosimilar (Brabio) any (g) Cladribine tablet (Mavenclad) relapse (h) Ocrelizumab (Ocrevus) other (i) Alemtuzumab (Lemtrada) UTI (j) Alemtuzumab (Lemtrada) bacterial.

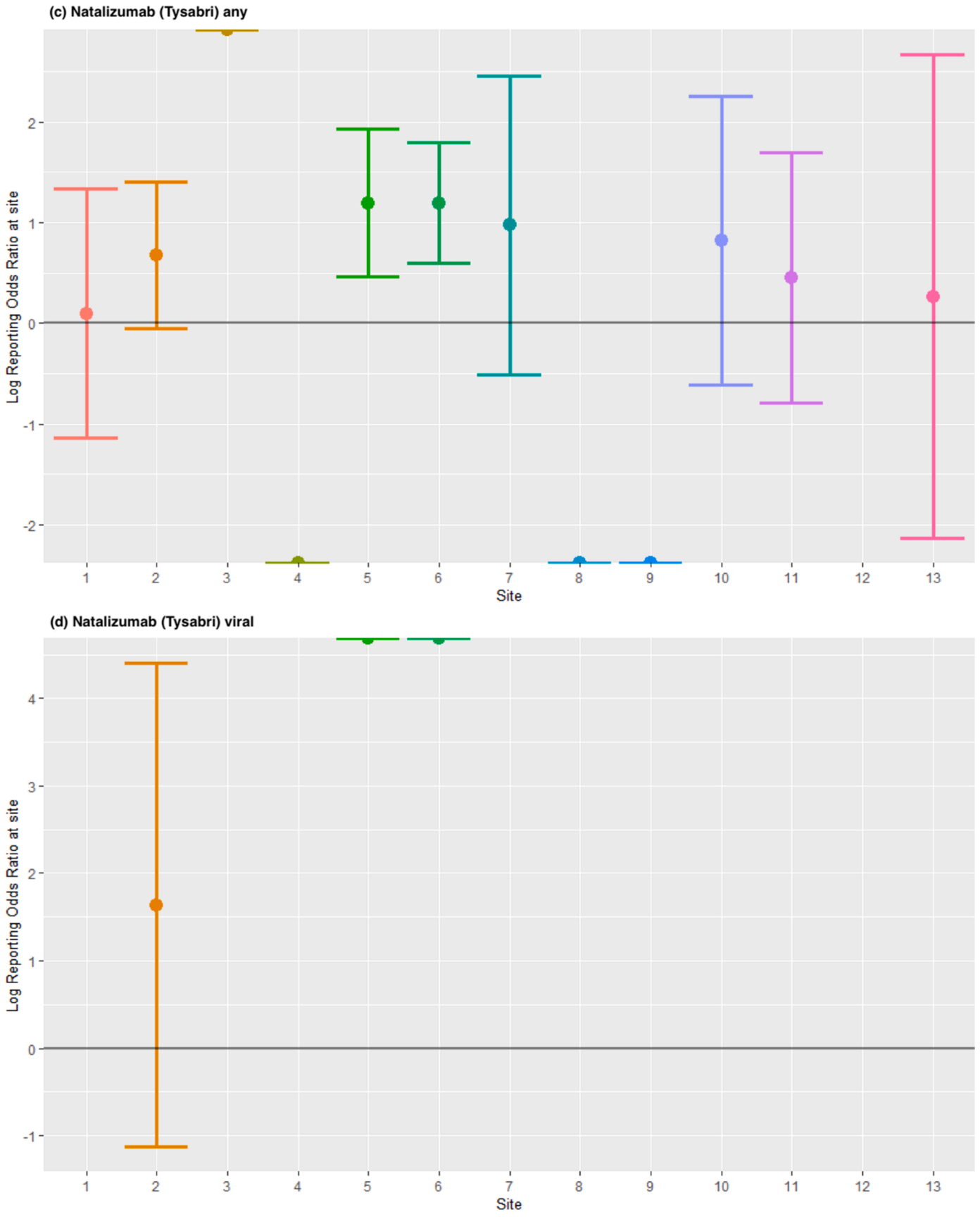


**Fig. 2.** (*continued*).

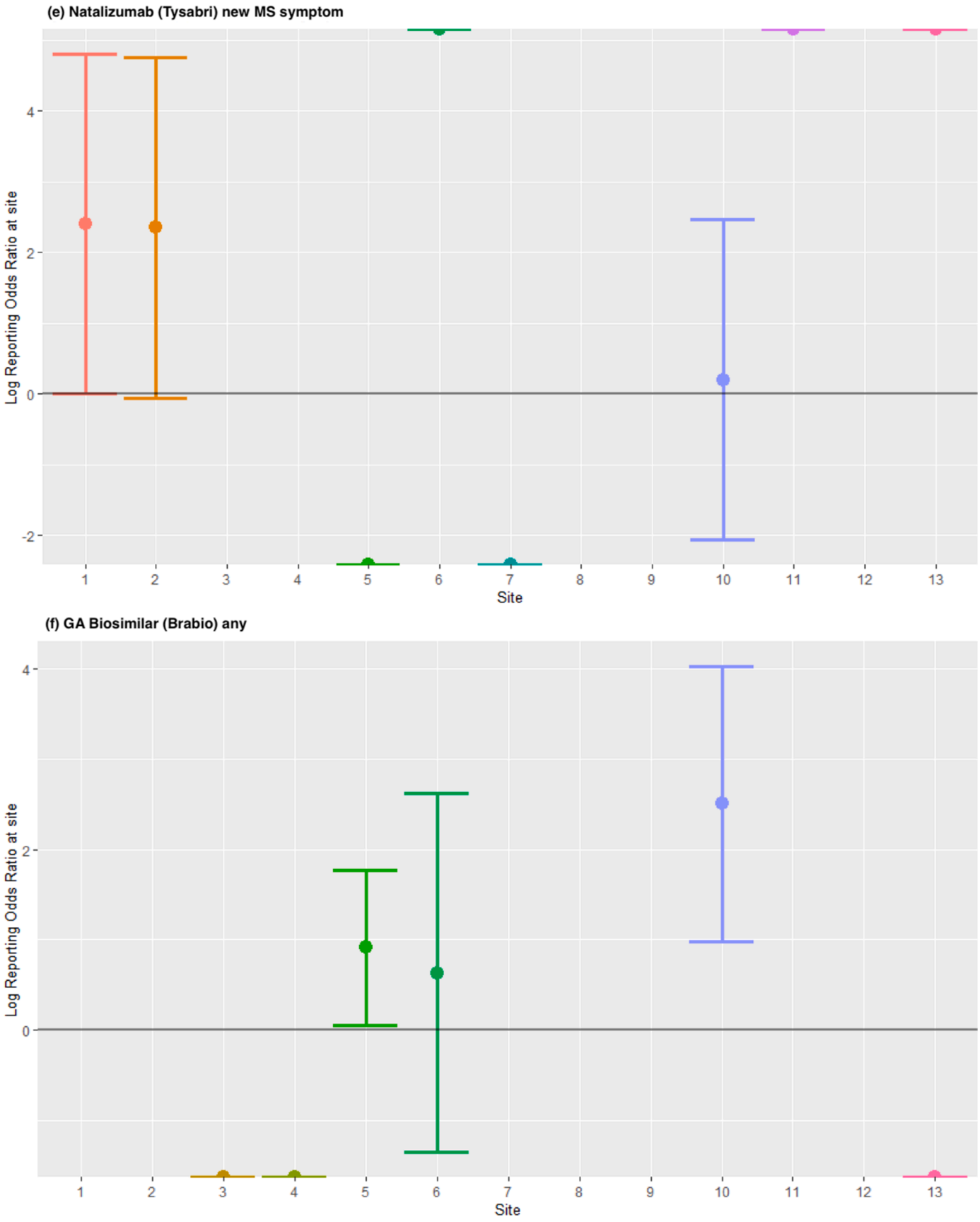


**Fig. 2.** (*continued*).

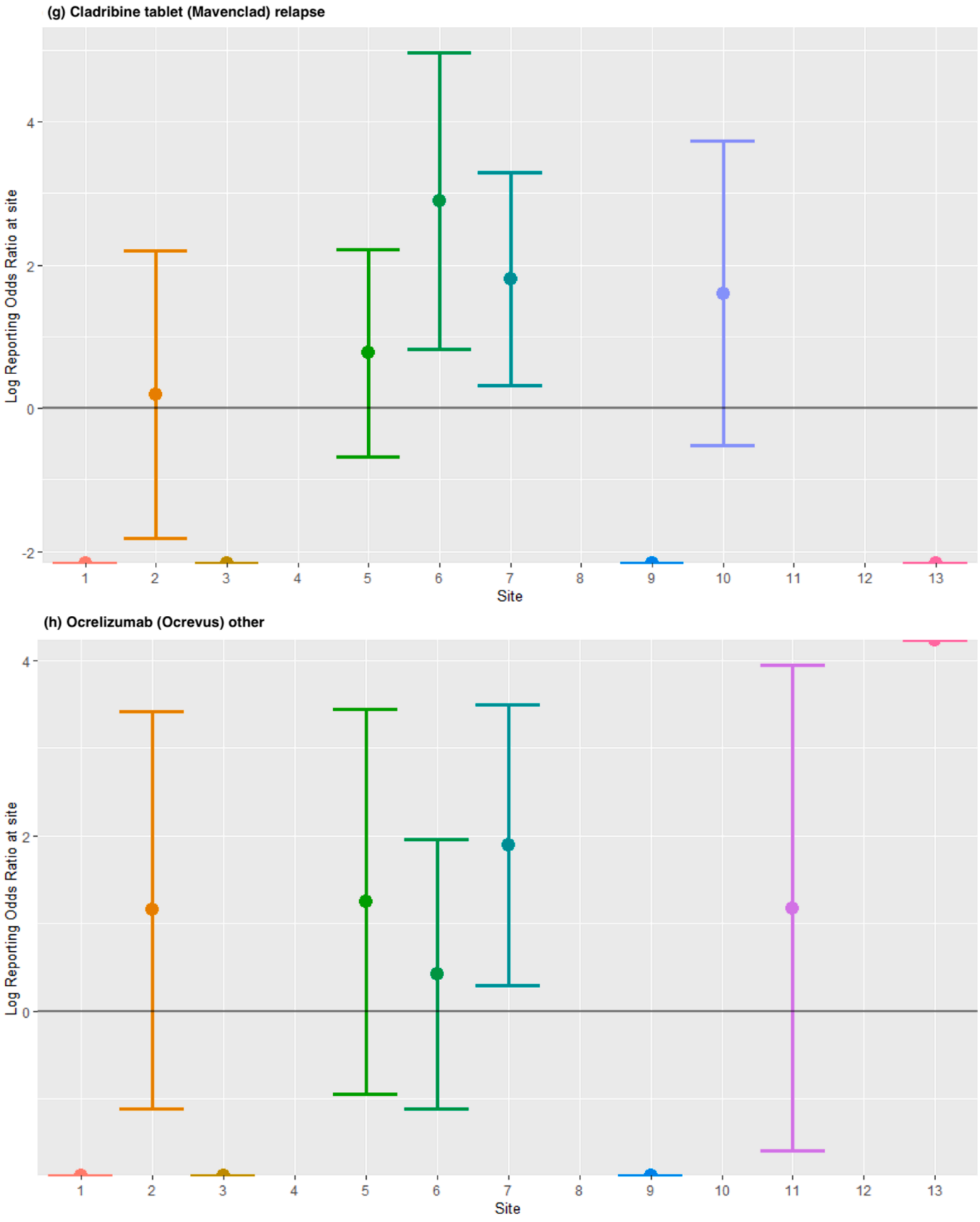


**Fig. 2.** (*continued*).

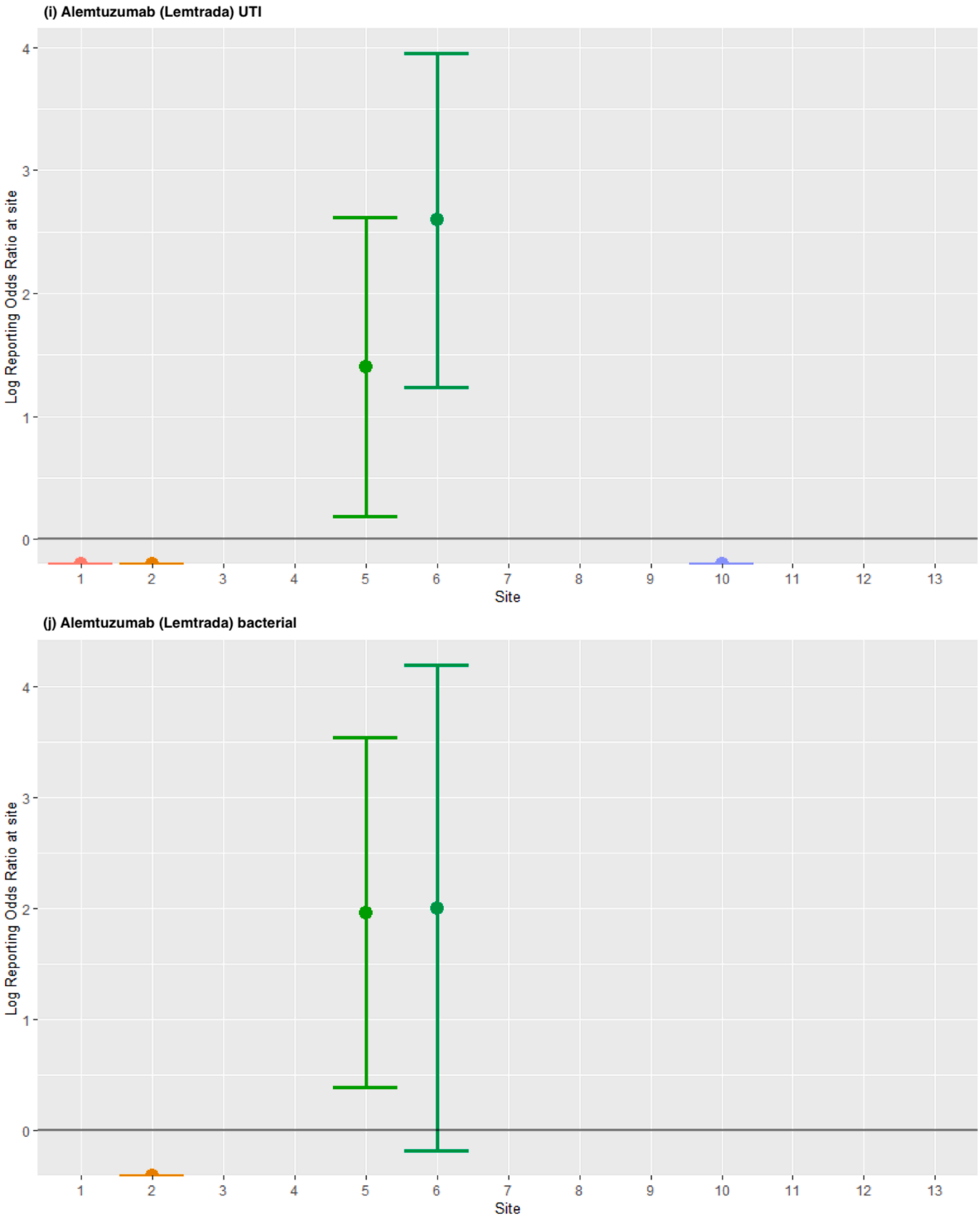


**Fig. 2.** (*continued*).

clear[14], an increasing proportion of people with MS are starting on highly active DMT, and so this bias may reduce over time. We have not included data on paraclinical tests including blood tests (lymphocyte count and liver function) and MRI data in this preliminary report. One of the primary long-term aims of the study is to examine the association between lymphopaenia and adverse events, however at the present time this study would not be sufficiently powered to look at this across different DMT considering the relatively short follow-up duration thus far. Similarly, the MRI data thus far is not sufficiently longitudinal to draw reliable conclusions.

A number of limitations arise from the real-world nature of the data used in this study. Differentiating MS relapses from transient symptom worsening can be difficult, and this difficulty has been exacerbated by the reliance on remote assessment from 2020 onwards. MRI monitoring protocols have been subject to rapid change as a result of the COVID-19 pandemic, with substantial variation in services both over time and between centres. Cross-validation using other similar studies is a useful technique to establish data reliability, however to the best of our knowledge no other real-world studies have a specific focus on the safety of DMT.

There is a suggestion from the current data that visit and monitoring frequency has the potential to substantially bias the reporting of common adverse events, and this will need to be cautiously considered. Furthermore, monitoring approach and intensity varies both between DMT, between sites, and also over time – not least as a result of limitations brought about by the COVID-19 pandemic. Managing this limitation is a real concern for all real-world data studies, and it is only via detailed study of disaggregated data that limitations can be truly understood. Controlling for site helps to address one aspect of these concerns, however future analyses with larger, longitudinal datasets will allow us to explore time-dependent effects, as well as to better estimate site-specific effects. A loss of power in the adjusted analyses due to low numbers on selected DMT at each site is a concern; power will improve in future analyses as more data is accrued at each site. It is important to note that these limitations are anticipated to be less of a concern for rare and severe adverse events, which are a major concern for both neurologists and people with MS.

Whilst, in this early analysis, we were not able to detect significant numbers of rare and/or serious adverse events, we have shown that we are able to detect significantly different risk profiles in patient populations treated with different DMTs. This paper demonstrates the potential of real-world data to understand not only the potential benefits associated with DMT (Kalincik et al., 2021), but also the ability of these data to help us better inform treatment-associated risks and hence inform the risk-benefit conversations that people with MS need.(Figs. 1 and 2).

## Author contributions

RD, MC and PMM co-designed the study. EW, AM and JP performed quality control and core analyses. RD drafted the manuscript. All authors reviewed, contributed to serial revisions and approved the manuscript.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.103894.

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