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# Neuropsychiatric symptoms in Systemic Lupus Erythematosus: mixed methods analysis of patient-derived attributional evidence in the international INSPIRE project

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## ABSTRACT

**Objective**: Attribution of neuropsychiatric symptoms in systemic lupus erythematosus (SLE) relies heavily on clinician assessment. Limited clinic time, variable knowledge, and symptom under-reporting contributes to discordance between clinician assessments and patient symptoms. We obtained attributional data directly from patients and clinicians in order to estimate and compare potential levels of direct attribution to SLE of multiple neuropsychiatric symptoms using different patient-derived measures.

**Methods**: Quantitative and qualitative data analysed included: prevalence and frequency of neuropsychiatric symptoms, response to corticosteroids, and concurrence of neuropsychiatric symptoms with non-neuropsychiatric SLE disease activity. SLE patients were also compared with controls and inflammatory arthritis (IA) patients to explore attributability of neuropsychiatric symptoms to the direct disease effects on the brain/nervous system.

**Results:** We recruited 2,817 participants, including 400 clinicians. SLE patients (n=609) reported significantly higher prevalences of neuropsychiatric symptoms than controls (n=463) and IA patients (n=489). SLE and IA patients' quantitative data demonstrated multiple neuropsychiatric symptoms relapsing/ remitting with other disease symptoms such as joint pain. Over 45% of SLE patients reported resolution/improvement of fatigue, positive sensory symptoms, severe headache, and cognitive dysfunction with corticosteroids. Evidence of direct attributability in SLE was highest for hallucinations and severe headache. SLE patients had greater reported improvement from corticosteroids (p=0.008), and greater relapsing-remitting with disease activity (p<0.001) in the comparisons with IA patients for severe headache. Clinician and patients reported insufficient time to discuss patient-reported attributional evidence. Symptoms viewed as indirectly related/non-attributable were often less prioritised for discussion and treatment.

**Conclusion**: We found evidence indicating varying levels of direct attributability of both common and previously unexplored neuropsychiatric symptoms in SLE patients, with hallucinations and severe headache assessed as the most directly attributable. There may also be - currently under-estimated - direct effects on the nervous system in IA and other systemic rheumatological diseases.

Key messages:

- Some common neuropsychiatric symptoms may be more directly attributable to SLE (and other systemic autoimmune rheumatic disease (SARD)) activity than previously assumed.
- Attributional rules should avoid unconditional exclusions, and not replace full exploration of patients' symptoms/views/history.
- Immunosuppression may reduce fatigue and other life-changing SLE (and possibly other SARD) neuropsychiatric symptoms not often specifically targeted for treatment.

**Key words**

Neuropsychiatric lupus, SLE, NPSLE, CNS lupus, patient-clinician interactions, misattribution, attribution, diagnosis, biopsychosocial, mental health, inflammatory arthritis, autoimmunity, rheumatology

## Introduction

There is a high prevalence of a wide range of neuropsychiatric symptoms in SLE [1, 2]. These symptoms can be caused by direct effects of the disease on the brain/nervous system, most commonly referred to as neuropsychiatric lupus (NPSLE) [3, 4]. However, there are other aetiologies which can occur in isolation or often in "difficult to disentangle" [5] combinations. These can include: the indirect impact of living with a chronic debilitating disease [5], pre-existing/co-morbid neurological and psychiatric conditions, infections, and the neuropsychiatric effects of medications, particularly corticosteroids [6].

The common exclusion of patients with NPSLE from randomised controlled trials for SLE has limited knowledge acquisition [7, 8]. Correct attribution is essential to facilitate appropriate treatment, yet aetiology is poorly understood, and diagnostic tests are often unenlightening [1, 3]. Assessment and attribution are therefore currently largely reliant on clinician opinion [2]. Our previous research identified that this is unlikely to reflect the extent of patient symptoms due to the under-eliciting, under-reporting, and under-recording of NP symptoms [1]. Under-estimating of subjective neuropsychiatric symptoms has been found in other diseases, with, for instance, oncologists correctly identifying less than 20% of their clinically anxious and/or depressed cancer patients as such [9].

Further limitations in NPSLE research and care arise from: 1) using only the limited range of neuropsychiatric manifestations in the ACR NPSLE classification [10]; 2) limited multi-disciplinary collaboration [1]; 3) Limited/non-inclusion of patients in decision-making on rheumatologist-dominated clinical guidelines committees [10], research teams [2, 11], and in care [12]; and 4) the reporting of unexpectedly low prevalences by the Systemic Lupus Inception Collaborating Clinics (SLICC) which has influenced research and clinical expectations. For example, SLICC reported rates of cognitive dysfunction (4.5%) and anxiety disorder (5.7%) [11] were lower than other SLE study results (e.g. cognitive dysfunction at 30-75% [13] and anxiety at 60-70% [1]), and lower than the general population [14].

Study criteria also exclude certain NP symptoms for various reasons, including on the grounds that they are common in the general population [2, 11] thus less specific for SLE. As their prevalence is significantly greater in SLE than in healthy controls [1], and these symptoms can be life-changing, unconditional exclusion rules are a concern as common symptoms may be directly attributable to SLE in some patients, and therefore responsive to immunosuppression. To address these limitations, we collected multiple types of data (such as response to corticosteroids) directly from patients, to assist in assessing attribution of a broad range of symptoms to the direct effect of SLE on the nervous system. These patient-reported attributional results have different strengths and limitations from clinician assessments, and may provide vital attributional evidence.

The aim of this study was to estimate - and compare - the varying levels of direct attribution to SLE of multiple NP symptoms using multiple patient-derived measures.

## Methods

## INSPIRE Project

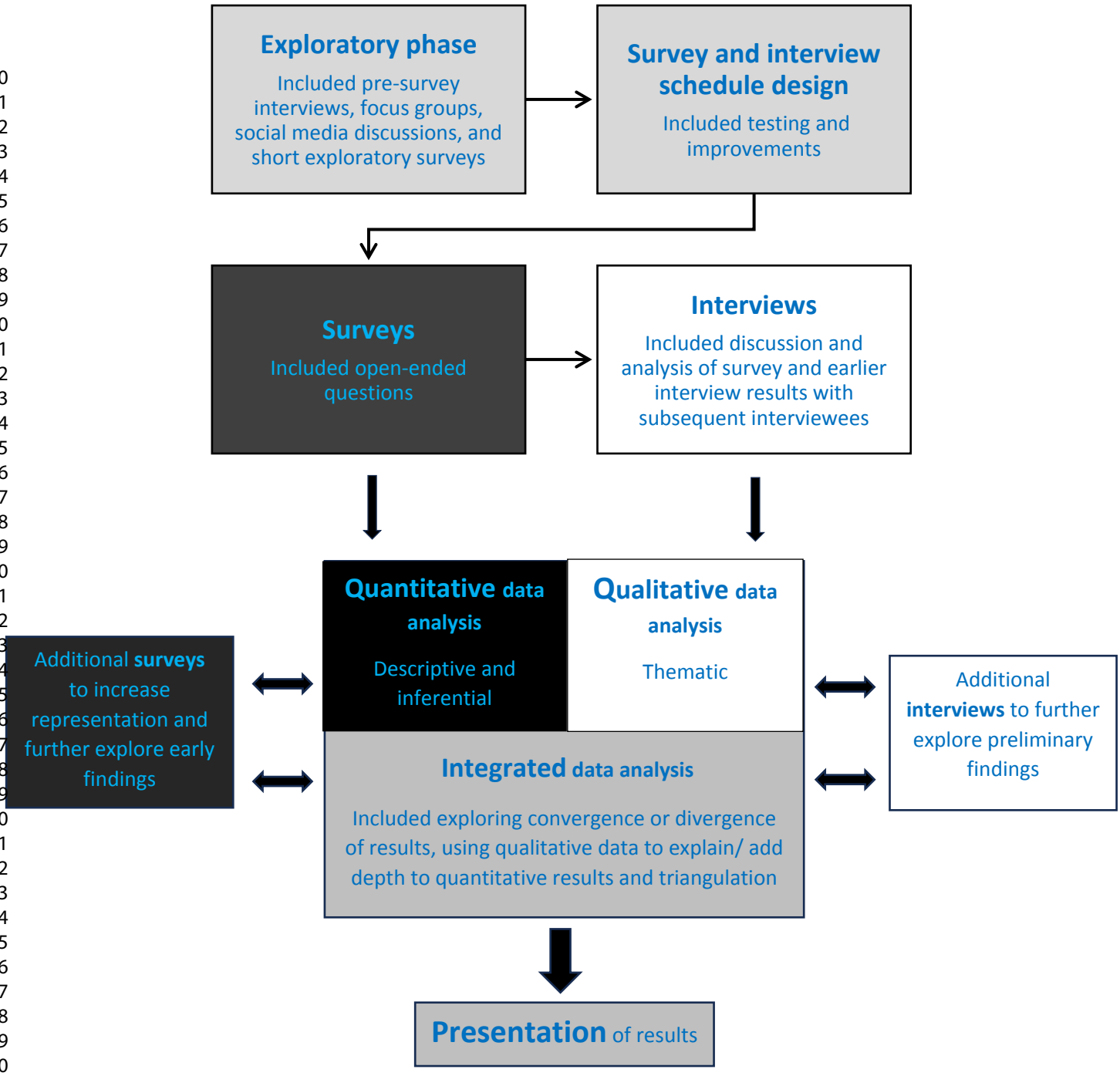
This study is part of the mixed methods INSPIRE (**I**nvestigating **N**europsychiatric **S**ymptom **P**revalence and **I**mpact in **R**heumatology patient **E**xperiences) research project which has been investigating (with patients and clinicians) various aspects of SARD NP symptoms. The first three INSPIRE papers have been published and focused on: investigating the prevalence and identification of NP symptoms[1], nightmares and hallucinations[15], and prioritising of evidence in diagnosing NPSLE[16].

### Study design

The INSPIRE research project utilises a form of multistage mixed methods [17, 18]. As depicted in Figure 1, data collection was sequential, utilising both *exploratory*[19] (where pre-survey interviews informed survey content) and *explanatory* (where post-survey interviews further explored and explained the quantitative findings) sequential methods[18]. Quantitative and qualitative analyses were initially conducted in parallel, followed by an integrated analysis period. Interviews also give our participants a "voice" and ensure that the human dimension – and often the suffering - is not overlooked within the statistics. Integration of both methods reduces the weaknesses that can arise from research using solely qualitative *or* quantitative data[18] and assists in the development of "nuanced and comprehensive findings"[20]. Further details on methodology can be found in supplementary information 1.

**Fig 1 – Study design flowchart demonstrating the integration of methods at each stage.**

White represents purely qualitative methods, black represents purely quantitative methods, with varying shades of grey representing differing dominance of either method at each stage.




## Study population and recruitment

Although SLE patients were the focus of this INSPIRE sub-study, other systemic autoimmune rheumatic disease (SARD) groups were recruited for the overall INSPIRE project, and acted as comparison groups for this paper's prevalence reports. All patients and controls were 18 years or over, in addition to patients reporting a SARD confirmed on clinical correspondence. Physicians were excluded from the INSPIRE study if they had not commenced specialty training.

Recruitment to the study commenced in July 2022. Surveys were available internationally via Qualtrics on social media, patient support groups and professional networks. Shorter surveys were made available in 2023 to increase representation of under-represented groups and obtain additional data on areas found to be of importance in earlier analyses.

**Selection of comparison group**

IA patients were selected as the comparison group following exploratory interviews and focus groups with rheumatologists, where the prevailing view was that there is no/ less direct impact of the disease on the nervous system in IA. As they also experience the physical and psychological stress of a chronic illness, a broadly similar proportion of indirect "reactive" symptoms such as depressive disorder would be anticipated[5]. Comparing SLE with inflammatory arthritis (IA) patient data, in-line with previous studies [5], may therefore enable more differentiation between direct and indirect attribution to the effects of SLE on the nervous system.

**Survey development**

Symptoms were selected for survey inclusion on pragmatic and/or phenomenological grounds, and on the basis of extensive pre-survey patient and clinician consultation, rather than to represent any fixed notion of aetiology or mechanism.

Identical lay terminology and explanations were used for patient, control, and clinician surveys. During the development phase, the survey was trialled (n=9) by using the 'think aloud' cognitive interviewing technique [21] to identify any areas of potential misunderstanding or confusion. Patients and controls were asked for their life-time frequency of each symptom from five options ranging from "never" to "always". Current health was self-assessed using validated instruments for depression (PROMIS SF8b) and anxiety (GAD-7) [14], and by single-item questions asking for assessment from 0-100 for each of: level of disease activity, fatigue, pain, and cognitive dysfunction. In addition, patients were asked multiple follow-on questions (supplementary information 2, section 1) for each symptom they reported experiencing >3 times. These are detailed in Table 1 in conjunction with limitations of the published literature and our methods to address these. Self-reported response of symptoms to corticosteroids was selected to estimate the effect of immunosuppressive medication. The focus on corticosteroids was due to their rapid action enabling a potentially more accurate self-interpretation of medication response compared to other common SLE medications, such as hydroxychloroquine and disease modifying anti rheumatic drugs (DMARDS), which may take several months to have a noticeable impact on symptoms.

**Interviews**

Interviewees were purposively selected from consenting survey respondents to ensure that a range of socio-demographic characteristics, disease groups, specialities, and opinions were represented. Interviews were conducted by three experienced medical researchers with a range of socio-demographic characteristics. Interviews were generally via Zoom, and were audio recorded and transcribed verbatim. Duration was most frequently between 30 minutes and 1 hour for clinicians and >1 hour for patients. A minority (n=4) of interviews were face-to-face, and n=20 (12 patients and 8 clinicians) interviews were via email.

**Further data integration**

Aside from the first interviews, the majority of interviewees were provided with study findings in the form of graphs, figures and/or anonymised quotes from earlier interviews. This enabled us to gauge clinician's and patient's reactions to the findings and to discuss the views of the other party in medical relationships, and for these to be included within the qualitative analysis. This is in line with our constructionist [22] and inclusive ethos. where we work collaboratively with participants [22]. During analysis, triangulation of qualitative and quantitative results, member checking initial results with participants, and discussion of conflicting views reduced threats to validity.

### Analysis

Associations between variables of interest were generated using chi-square tests, Spearman's Rank or Pearson's correlation coefficients as appropriate. T-tests were used to investigate potential between-group differences in continuous or ordinal variables of interest. Logistic regression models, adjusted for age, gender, country and ethnicity, were previously used to calculate the odds ratios and the 95% CI of lifetime (experienced >3 times in life) prevalence of neuropsychiatric symptoms among SARDs groups and control participants[1]. Frequencies and percentages were used to describe the data. Certain symptoms were excluded from the attributional estimate analyses. This included if they were experienced by too few patients (e.g. seizures) or misunderstandings in defining the symptom had been identified (e.g. weakness had been confused with fatigue in some cases).

The 23 NP symptoms were initially ranked in order of direct attributability for each of the five measures of evidence from one being the least attributable symptom to 23 the most attributable. The mean (and SD) of the five rankings for each symptom were then calculated to give an overall ranking of potential direct attributability.

Data from interviews and open-ended survey questions were analysed thematically. For this study, each category was pre-decided (e.g. response to corticosteroids) and data for each category was analysed thematically. Stages of thematic analysis[23] included: 1) full immersion in the data; 2) developing a coding scheme, and subsequent coding; 3) combining participant transcript extracts for codes; and 4) discussion and agreement between the multidisciplinary study team and a selection of participants. Timing of symptoms in relation to disease onset generated extensive qualitative data and is covered in a separate INSPIRE paper.

### Patient-centred research

Key aims of all our studies are to represent the views/experiences of these patient and clinician groups, to give them a wider voice, and improve understanding, medical relationships, clinical care, and quality of life. An additional key ethos is that patient partners are an equal and valued part of our research teams and fully involved in every aspect of the research cycle. We also ensure that the wider patient population are regularly given opportunities (through questions and surveys on disease forums and support groups, and through focus groups) to be actively involved in our research, including in decision making about the research direction and the selection of symptoms for investigation.

## Ethical approval

The Cambridge University Psychology Research Committee provided ethical approval: PRE 2022.027. Informed consent was taken electronically on surveys and verbally (audio recorded) for interviews. The pre-registered protocol and statistical analysis plan can be found at: https://osf.io/zrehm .

Table 1

## Results

The total number of participants (Table 2) was 2,817. This included SARD patients (n=1954 surveyed, n=69 interviewed), controls (n=463), and clinicians (n=400 surveyed, n=50 interviewed). Most patients and controls were UK residents in addition to most patients being female (90%). Further sociodemographic and disease details can be found in supplementary information 2, Table A1.

**Table 2**

Results are divided into categories of attributional evidence data incorporating: 1) Comparison of NP symptom prevalence between SLE, other SARDs, and controls; 2) NP symptom correlations; 3) Response of NP symptoms to immunosuppressive treatment; 4) Relapsing/remitting of NP symptoms with other SLE disease symptoms; and 5) Overall mean rankings for measures of potential direct attributability**.**

### Comparison of NP symptom prevalence between SLE, other SARDs, and controls

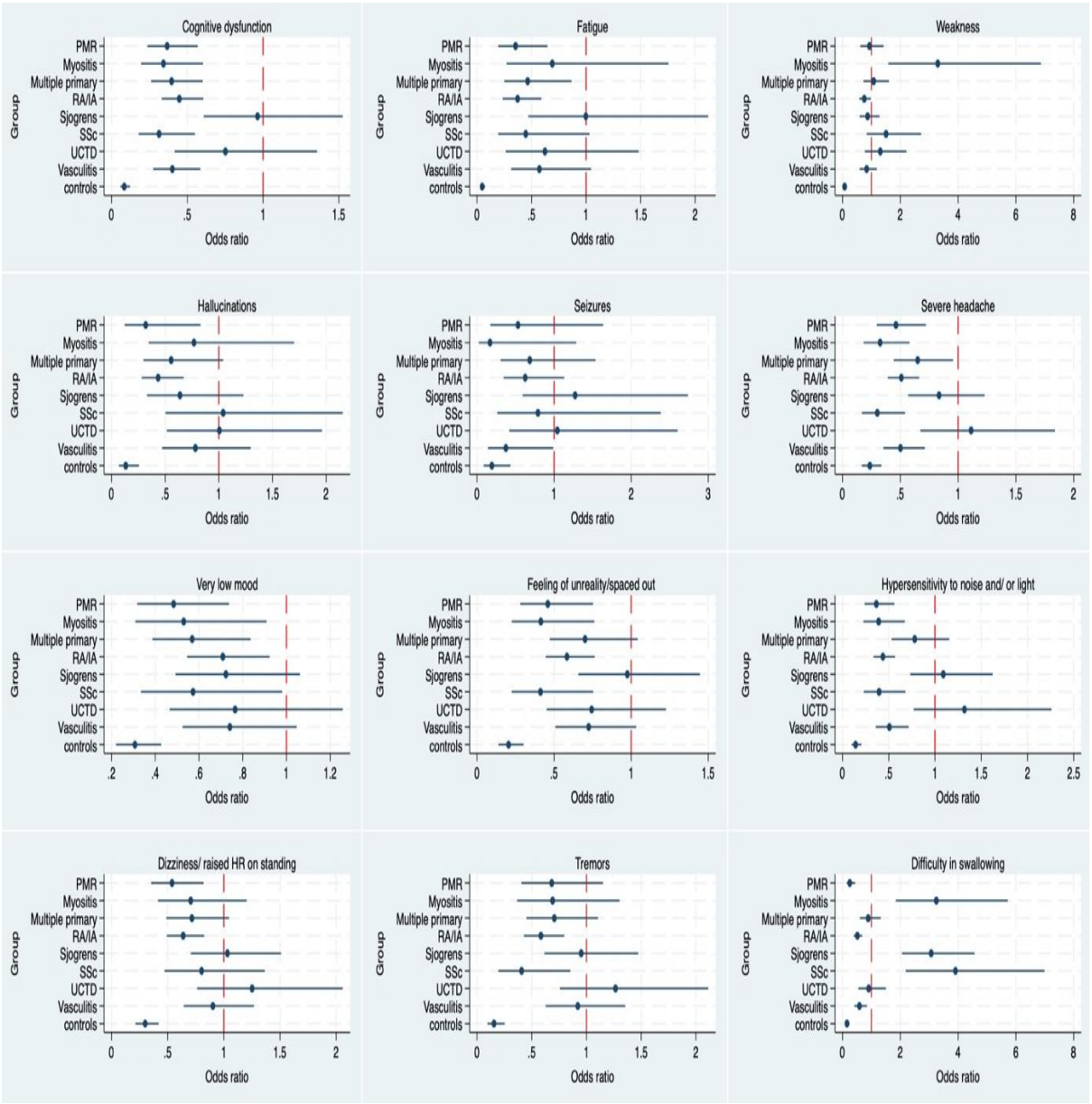
SLE patients experienced a mean of 14 (SD 6) of the 30 NP symptoms listed on the survey, compared to 11 (SD 6) in IA/RA patients and 5 (SD 5) in controls. SLE patients had significantly higher odds of experiencing each NP symptom than controls (all $p<0.001$) (Figure 2). When compared to IA patients, SLE patients also had significantly higher odds of lifetime prevalence (Table 3, column 1) of almost all NP symptoms (see Table 3 for individual symptom statistical significance). Interviews revealed a similar psychiatric burden of coping with a chronic disease between SLE and IA patients, and the negative impact of medications on NP symptoms was considered by rheumatologists to be broadly similar. Increased prevalence in SLE was discussed by clinician interviewees as therefore likely reflecting a greater degree of attribution to the direct effects of the disease on the nervous system.

Although some clinicians were sceptical about the accuracy of patient-reported data, other clinicians when shown the figures noted that "difficulty swallowing" having the highest OR for myositis, Sjögrens and systemic sclerosis, and "weakness" in patients with myositis (Figure 2) demonstrates that patient reported symptoms can have good accuracy and face validity, at least for comparison, as a higher prevalence would be expected by their respective disease mechanisms.

Concerns were expressed by some clinicians that the range, prevalence and direct attributability of some NP symptoms are frequently higher in clinical practice than those often reported in large influential studies, including most notably those from Systemic Lupus Inception Collaboration Clinics (SLICC). The deleterious effects of excluding common symptoms from attribution models was also highlighted:

> *Some like depression, anxiety and the headaches…They are a part of the lupus though and we see them much more in lupus patients…they do better if they are treated with the immunosuppression…they should be part of the attribution models because they are parts of it and if they aren't included then they may not be properly treated….these symptoms are a direct manifestation of the lupus.* (Ppt 200, rheumatologist, Europe)

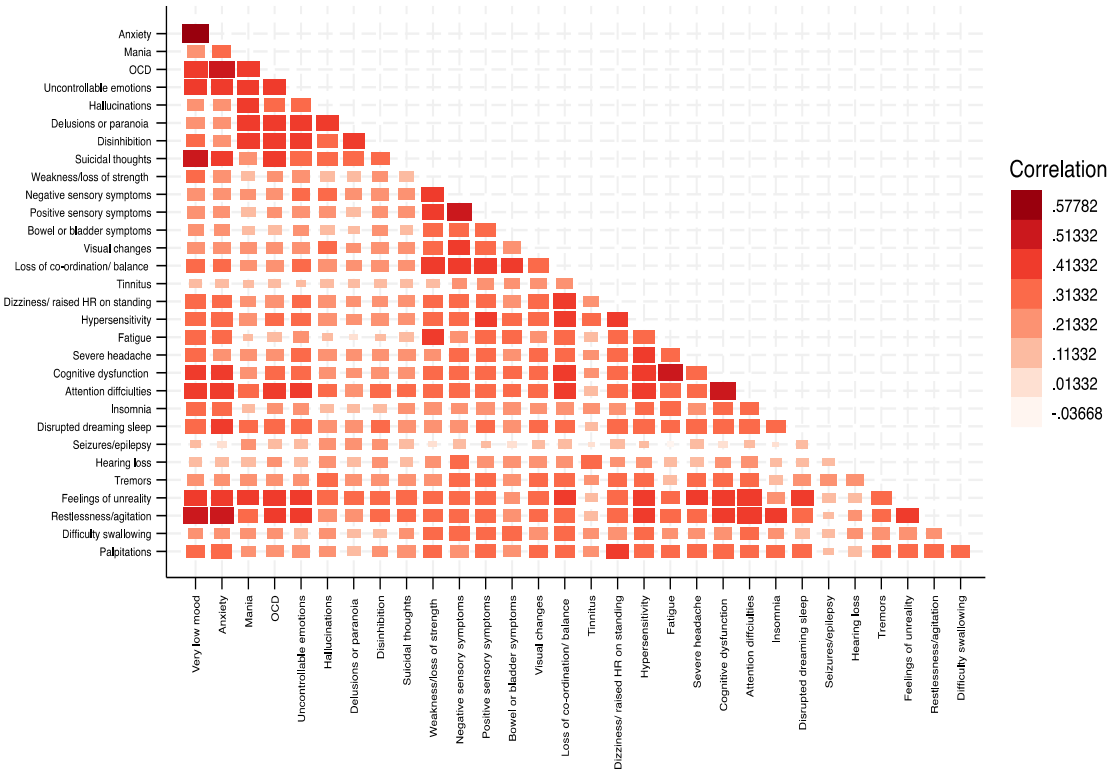
Figure 2 – **Odds ratios of lifetime (experienced >3 times in life) prevalence of neuropsychiatric symptoms among SARDs groups and control participants compared with SLE.** Adjusted models using SLE as the reference (vertical red line). Additional symptom graphs can be found in supplementary information 2, figures A1 and A2.



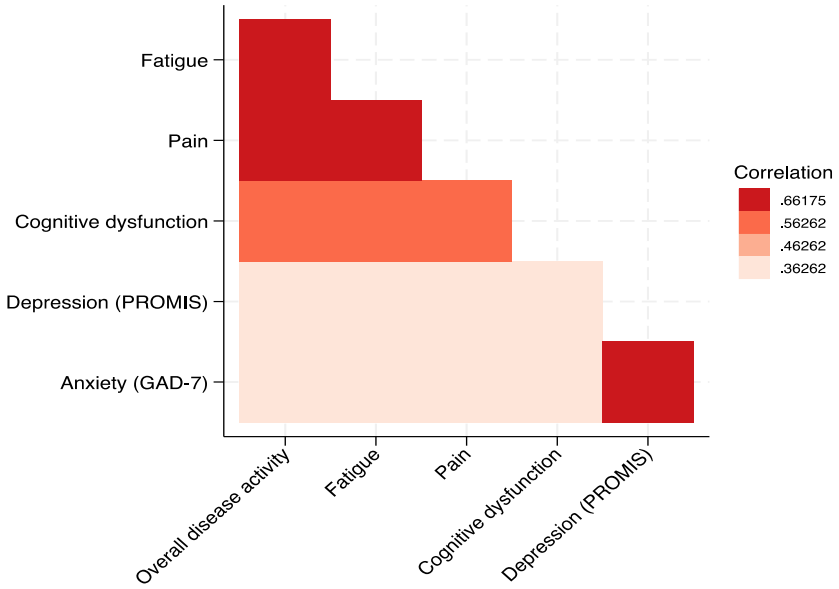
**NP Symptom correlations**

There were multiple correlations between symptom frequencies as shown in Figure 3a, including between psychiatric and neurological symptoms. Correlations between mood and anxiety disorders (such as a correlation of $r=0.49$, $p<0.001$, between very low mood and anxiety), and associations between the more severe psychiatric symptoms, were as expected. Interestingly, two of the symptoms suggested for inclusion in the study by patient groups, "restlessness/agitation" and "feeling of unreality/spaced out", were equally or more correlated with the other symptoms than some of those more commonly associated with NPSLE. Patient self-assessed current levels of disease activity (Figure 3b) were more highly correlated with pain ($r=0.69$) and fatigue ($r=0.62$), than with depression ($r=0.34$) or anxiety ($r=0.31$). Fatigue was more highly correlated with pain ($r=0.58$) than with depression ($r=0.37$) (all listed correlations $p<0.01$).

**Figure 3 A** (Darker and larger boxes signify larger correlations)




**B**



Symptom frequency correlations and current disease activity. **(A)** Correlations between frequency of NP symptoms experienced by SLE patients **B)** Correlations of self-assessment of current overall disease activity, pain, fatigue, and validated assessment instrument scores

**Response of NP symptoms to immunosuppressive treatment**

A positive symptom response to corticosteroids was widely considered by clinicians to be indicative of the symptom being inflammatory and attributable to the direct effects of the disease. The exception was fatigue where improvement was felt to sometimes be more related to the temporary increased energy from corticosteroids. Symptoms reported by SLE patients as being the most responsive to resolving/reducing on corticosteroids were fatigue, hallucinations, positive sensory symptoms, feelings of unreality, and severe headache (all improving in >50% of SLE patients), and cognitive dysfunction in 47% (Table 3, column 2). Interviews also revealed multiple reports of great improvement in these symptoms when treated with corticosteroids and with DMARDs:

> *While unmedicated I tried to complete post graduate study and had to give up. I couldn't seem to synthesise information. Since re-starting medication I have completed two degrees and graduated in the top 10% of graduates. Medication makes all the difference.* (Ppt 1456, SLE, Australia)

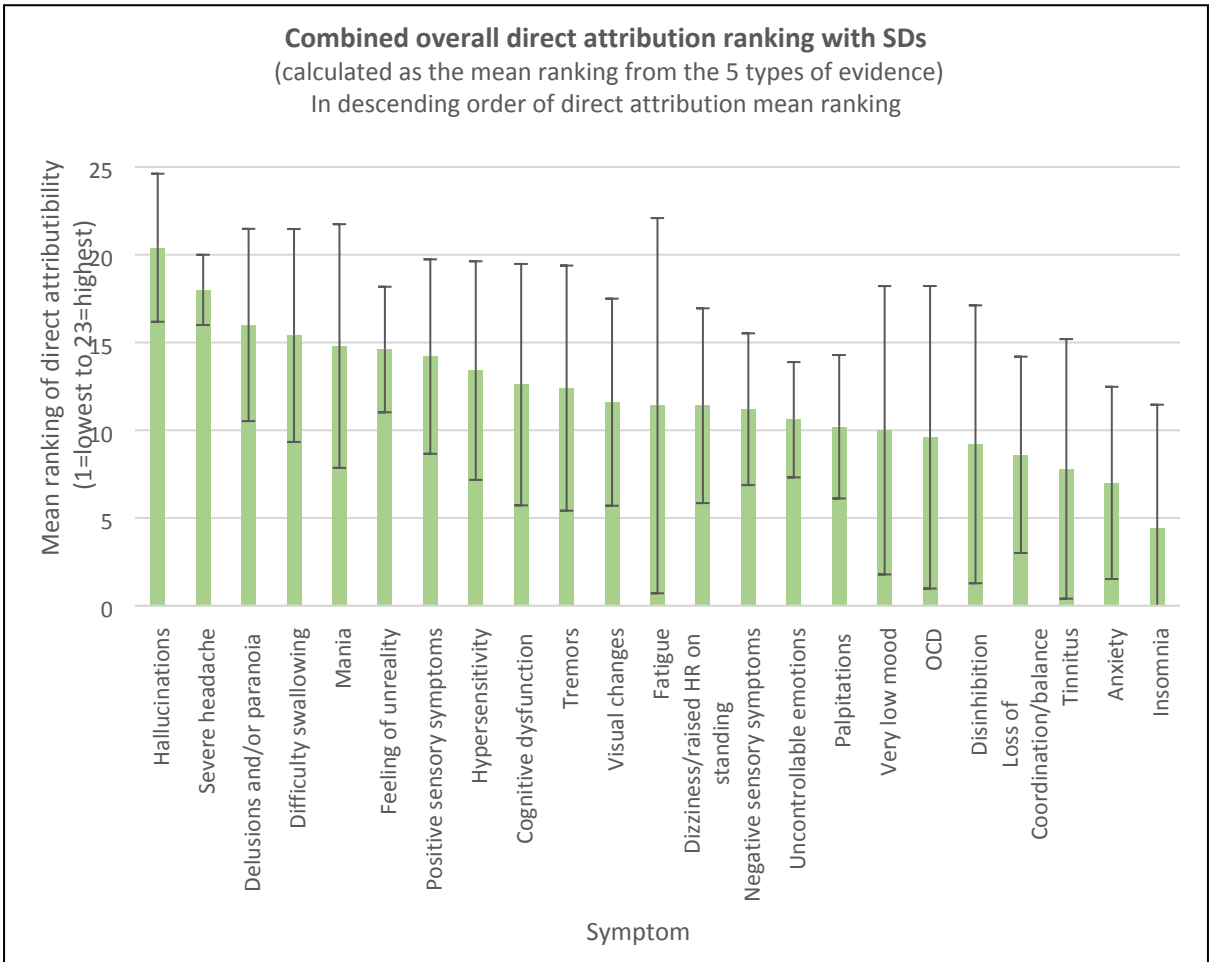
A positive response to medication was also reported for symptoms often considered to be more a reaction to a chronic disease than directly attributable to the disease itself: "*We have had several with severe depression and suicide ideation, and they've responded very well to immunosuppression"* (Ppt 53, rheumatologist, India). Although most NP symptoms were not routinely monitored or directly treated, several clinicians observed that patients who had had organ-threatening disease aggressively treated with biologics such as rituximab, and/or cyclophosphamide, were subsequently less likely to report cognitive and fatigue symptoms in clinic. They generally perceived this as evidence that these symptoms are also responsive to immunosuppression and thus have a level of direct attributability. However, it was also acknowledged that some symptoms will also improve with reductions in disease activity through indirect mechanisms, such as improved mood and increased ability to participate in social and physical activity.

Other clinicians felt that these 'non-specific' symptoms will not respond to immunosuppression. This view was more frequently expressed by clinicians reviewing <5 SLE patients per annum, who were extrapolating their experience of the response of other disease groups and their general assumptions regarding attribution: "*We know that treating these non-specific symptoms like fatigue and brain fog doesn't actually have any effect so that's more evidence really* [against direct attribution]" (Ppt 66, neurologist, England). When shown the data demonstrating evidence of a response to corticosteroids, several neurologists surmised that subjective symptom improvements were due to placebo effects, although they acknowledged that placebo effects should be similar among SARD disease groups. Significantly higher numbers of SLE than IA patients reporting positively responding to corticosteroids for some NP symptoms, including severe headaches (p=0.008), dizziness/ raised heart rate on standing (p=0.01) and hallucinations (p=0.047) may suggest a greater degree of direct attributability of these symptoms in SLE. Clinicians from all specialities considered that NP symptoms were more frequently directly attributable in SLE than in the other SARDs, but reports of improvements on medication were also frequent in other SARD patients:

> *I think that mental health problems are definitely a direct effect of the disease. I was previously prescribed adalimumab which I injected every two weeks and my mental health symptoms were always far worse at the end of the fortnight, when the effects of the medication were starting to wear off. I was always fine for about a week from the day after the injection* (Ppt 1058, RA, England)

**Table 3**

**Fig 4 –Overall mean rankings for measures of potential direct attributability in SLE for NP symptoms.**




**Method of calculating overall attribution ranking**

Each of the 23 symptoms included were ranked in order for each of the 5 types of evidence listed below from: 1=lowest ranking of level of direct attributability to 23 = highest. The mean (and SD) of the 5 rankings were then represented in the graph above.

**Types of evidence used to estimate and compare level of direct attributability in SLE (from Table 3)**

1. Percentage of SLE patients reporting improvement/resolution of symptom with corticosteroids

2. Percentage of SLE patients reporting the symptom relapsed-remitted with other symptoms

3. Comparison of % of SLE patients reporting improvement with corticosteroids compared to % IA patients reporting improvement with corticosteroids (SLE % / IA %s for each symptom)

4. Comparison of % of SLE patients with % of IA reporting symptom relapses- remits (SLE % / IA% for each symptom)

5. Comparison of SLE symptom prevalence with IA prevalence for each symptom (SLE % /IA% for each symptom).

**Relapsing/remitting of NP symptoms with other SLE disease symptoms**

Whether each NP symptom relapsed/ remitted with other SLE disease symptoms was considered to be strong evidence of direct attributability, particularly by rheumatologists and patients. With SLE, this was reported most often for fatigue (79%), very low mood (70%) and cognitive dysfunction (66%) (Table 3, column 3). Patients frequently identified that anxiety and depression increasing in a flare may sometimes be more a reaction to feeling unwell than directly attributable to SLE. Although much less intuitive and acceptable to patients, several neurologists suggested that neurological NP symptoms, such as increased sensory symptoms, could also be indirectly related in some cases:

> *Just because a symptom relapses/remits, it doesn't always mean it's pathological, it may simply be because you've got pain in your joints at that time, then you're paying more attention to your body, then you're more likely to experience other symptoms too* (Ppt 46, neurologist, England)

However, this was felt to be a less likely explanation in the case of some patients' descriptions of neurological and/or psychiatric symptoms at the start of, or just preceding, a flare.

Clinicians had diverse views on the relationship of fatigue with other SLE disease activity symptoms, with some considering it multi-factorial in many patients, and often persisting in the absence of other disease features. Patients felt fatigue had a high level of direct attributability, and it was frequently the most life changing symptom, inducing feelings of being "*worthless", "a burden"* (multiple patients), and '*grief for the life lost'* (Ppt 611, SLE, Wales). The vast majority of clinicians were empathetic in interviews about the impact of fatigue and other NP symptoms on patient lives regardless of personal attributional views. However, they acknowledged that symptoms considered to be more life-threatening and/or known to be treatable by immunosuppression, often had to be prioritised when clinic time was limited. Clinicians and patients frequently reported that limited appointment times precluded sufficient exploration of NP symptoms and collaborative attempts to differentiate between causes.

**Overall mean rankings for measures of potential direct attributability in SLE**

Calculating an overall mean ranking of potential direct attributability for each NP symptom placed hallucinations and severe headache as the most directly attributable symptoms to SLE (of the 23 NP symptoms included), and anxiety and insomnia as the least (Figure 4). However, the frequently high standard deviations representing high variation between each measure's ranking of different symptoms indicated limited consistency between different types of attributional evidence. This demonstrates the presence of multiple confounders for different symptoms when using each of the different methods.

The rankings for the SLE specific measures (response to corticosteroids and relapsing-remitting with other disease symptoms) were positively correlated ($r=0.478$, $p<0.05$), yet were negatively correlated with some of the SLE/IA comparative test rankings.

## Discussion

We analysed neuropsychiatric symptom attributional evidence directly from, and with, SLE and other SARD patients. Our findings demonstrated multiple sources of evidence (such as response to immunomodulating medication) converging to indicate varying levels of direct attributability for multiple NP symptoms. We report similar findings to other SARD studies detailing improvements in a variety of NP symptoms with immunosuppression, including mood and anxiety [31], fatigue [32, 33], and psychosis [34]. The divergent views expressed by our participants regarding attribution were representative of existing research where some studies reported evidence of direct attributability [35], whereas others suggested that some symptoms may be more related to psychosocial influences [36], or multifactorial causes [37]. The symptoms with the highest combined evidence of potential direct attributability to SLE were hallucinations and severe headache, with insomnia and anxiety having the lowest evidence. However, these results should be interpreted with caution given the high variations in attribution rankings between each of the 5 types of attributional evidence included, and the multiple confounders and inaccuracies inherent in any current method of assessment of NP symptoms.

Fatigue was rated as the most directly attributable symptom by clinicians and patients in our previous study[12] and scored the highest in terms of the SLE specific attributional evidence acquired in this study. We also found a stronger association between fatigue and self-reported disease activity than between fatigue and depression. This is in accordance with studies demonstrating associations of persistent fatigue with chronic inflammation [38], but conflicting with other studies suggesting fatigue is more related to depression than disease activity [39]. Differences may be partially explained by the different measures used for disease activity, with our study using patient self-assessed measures compared to other studies using physician administered instruments such as the SLEDAI 2K [39], both of which are subject to different limitations. Using a clinician administered instrument incorporating a limited range of symptoms may result in under-estimations of disease complexity. More granular patient self-assessments allow for more nuanced individualised assessments yet may be more skewed to self-assessing the most life changing symptoms such as fatigue as indicating the most severe disease activity.

Consistent with research reporting limited sensitivity of the attribution models used in the SLICC NP studies[4], some clinicians expressed concern that the SLICC reports of NP symptom prevalence and attributability were much lower than among their own patients and in other research findings [1, 5, 13, 36]. It was felt that this could be contributing to more widespread under-identification, under-attribution and under-treatment of some NP symptoms, particularly in the potential for (mis)use of attributional "decision rules"[11] unconditionally excluding all cases of certain symptoms as directly related to SLE. This includes headaches which are a contested NPSLE symptom in the literature. Some studies report insufficient evidence of an association between headache and disease status [40], whereas other studies and clinicians consider multiple direct causes of severe headache in SLE patients including aseptic meningitis and headaches that respond to immunosuppression and not opiate analgesia [10]. Our data demonstrated some of the strongest evidence (compared to the other symptoms studied) of direct attributability for severe headache. This evidence suggests that unconditional rules/assumptions excluding all cases of certain symptoms as non-attributable solely due to being common in the general population as opposed to any medical or patient-specific rationale should be re-considered.

Furthermore, some clinicians were equating common, and "non-specific" with a high likelihood of non-attributability, yet symptoms which are non-specific in isolation can have high specificity when viewed in combination. Our data suggests that trials of immunosuppression may be of benefit in some cases for these non-specific symptoms. This includes for the highly prevalent and often most life-changing symptoms of fatigue [41] and cognitive dysfunction, both of which ranked highly in SLE specific attributional evidence. Although these symptoms had lower attribution rankings when comparing SLE with IA patient results, this may reflect similar levels (which may be high) of direct attributability in both diseases. The self-reported response rates to corticosteroids were lower for some other symptoms, emphasizing the need for caution to avoid overtreating. This observation doesn't challenge the causal link with the disease in many patients but highlights the potential that some NP symptoms in some SLE patients will include aetiologies beyond immune-mediated processes [42]. In

addition, given the potential adverse effects of corticosteroids, including on some psychiatric symptoms, any treatment decisions should be carefully balanced between attributional evidence and risk of harm.

Although some symptoms (e.g. tinnitus) had comparatively low evidence of direct attributability in our measures, a minority of patients reported that these symptoms had a positive corticosteroid response and/or relapsed/remitted with other disease manifestations. These symptoms may therefore be responsive to immunosuppression in some patients, and the probable lesser direct attributability to the disease at group level should not lead to assumptions of lack of direct attributability at individual level. Our data provides further support for the importance of assessing each NP symptom's attributability in each individual, and with full collaboration with the patient [12], and a multi-disciplinary team[35]. Combining attributional evidence from patient's reports and "attributional insights"[16] with clinician assessments and judicious use of diagnostic tests reduces the limitations of each area of evidence. This is particularly important in NPSLE where current neuroimaging and serological investigations are often normal[3, 16], and where many NP symptoms are not visible to clinicians and therefore detection is often reliant on patient reporting [16].

Our results are consistent with other studies demonstrating higher prevalences of NP symptoms in SLE compared to IA [39], and greater evidence of direct attributability of some NP symptoms in SLE. However, our results also indicated that IA and other SARD patients had higher NP symptom lifetime prevalences than controls, and multiple strands of evidence from both the quantitative and qualitative data indicated possible direct attributability of some NP symptoms in some IA patients. This is in accordance with the rapidly evolving knowledge of neuroinflammation which has increased understanding of biological plausibility [43]. This includes evidence of the relationships between autoimmunity and neuropsychiatric diseases [44], between peripheral inflammation and CNS symptoms [45], and higher frequencies of cognitive dysfunction, fatigue and/or mood disorders after sepsis [46], cancer [47], and infections such as Covid [48]. Indeed, it seems increasingly plausible that all SARDs will have some NP symptoms that are directly attributed to the effects of the autoimmune disease on the nervous system in some patients.

Although we have focused on assessing direct attributability for this study, indirect causes/exacerbators of neuropsychiatric symptoms were also frequently discussed, particularly the understandable distress and anxiety from coping with an unpredictable incurable disease. These symptoms were viewed by some patients and clinicians as being less important than symptoms considered to be directly attributable for discussion in time constrained consultations. Additional evidence of attributional hierarchies for discussion and treatment may include findings of worse outcomes for NP symptoms deemed non-attributable compared to those attributed to SLE [2]. Although this suggests that outcomes may improve with more recognition that NP symptoms may be directly attributable in some patients and treated with immunosuppression, utilising a more integrated biopsychosocial model [49] of attribution and support could also improve outcomes. Prioritising biological causal theories for psychiatric symptoms has been found to reduce patient support for lifestyle based treatments [50]. These interventions, and psychotherapies, can be highly beneficial in assisting people in adapting to life with chronic diseases and improving mental health [51], regardless of attributability to systemic illness.

Patient-clinician communication and collaboration is essential in ascertaining attribution and appropriate treatment for each NP symptom, yet clinicians reported being severely constrained in their ability to elicit NP symptoms. Constraints included insufficient clinic time for such complex multi-system diseases, compounded by patient reticence in disclosing NP symptoms and varied clinician knowledge of the range of potential symptoms to enquire about[1]. The process whereby the study interviewers facilitated the self- identification of the patient interviewee's attributional evidence often took >1 hour, which clearly is not feasible in busy rheumatology or neurology clinics. Longer appointment times are also required to facilitate patients and clinicians fully exploring each patient's attributional evidence together to determine the most likely cause(s) of each neuropsychiatric symptom. However, even with detailed questioning and combining quantitative and qualitative data, attributional evidence is subject to multiple confounders. For example, controlling the disease activity

with immunosuppression is also likely to improve QoL and therefore also reduce indirect, psychosocial or reactive symptoms.

General limitations of the INSPIRE project are detailed in the first INSPIRE paper [1], and include the self-selecting nature of online non-randomised recruiting. Patient self-assessments are accompanied by their own limitations including recall bias [25], no diagnostic tests for comparison, and the possible short-term euphoria and/or placebo effect from corticosteroids. In addition, structural damage such as from a stroke may be from the direct disease effect but will not resolve with corticosteroids or relapse/remit with other disease symptoms, reducing the accuracy of the attributional evidence we used for symptoms which may constitute permanent damage. Studies have also identified differences in self-interpretation of symptom severity by sociodemographic group [52]. Importantly, depressed patients may perceive their overall symptom burden as higher than those without depression [53]. Although we pre-published the study protocol and statistical analysis plan, the high quantity of comparative tests between IA and SLE patients for each symptom without correcting for multiple testing increases the risk of type 1 errors, and so estimated effects should be interpreted with some caution. The high variation in the symptoms' attribution rankings between the measures assessed indicates the limitations in using any one type of evidence individually to assess attribution. Although the rheumatologist participants in pre-survey interviews largely considered IA NP symptoms to not be directly attributable to the effect of IA on the brain, other speciality interviewees (and our SLE/IA comparative data) suggested that inflammatory/autoimmune processes may affect brain function in both conditions. There are also neuroimaging studies which indicate the influence of autoimmune disorders on brain function and explore the neurobiological mechanisms underpinning fatigue in IA[54]. Our selection of IA as a comparison group was therefore a significant limitation, and a more appropriate comparison group for future research would be a non-inflammatory chronic illness.

A strength of our study was in combining the multiple types of evidence to (somewhat) mitigate the inaccuracies of each source of evidence, which will vary by symptom and by attributional assessment methods. For example, mania may be directly attributable to the disease yet be worsened by corticosteroids and thus receive a low ranking for that criterion. Conversely, low mood may rank highly in terms of relapsing-remitting with other disease symptoms, yet in some patients be more related to feeling unwell in a relapse than be directly attributable. Additional study strengths are listed in our previous INSPIRE paper [1] and in table 1, and included involving study participants (clinicians and patients) in the interpretation of the data, in addition to the multi-disciplinary INSPIRE study team, thus allowing for multiple interpretations of a shared reality [22], and enhancing reliability and reducing threats to validity.

In conclusion, the attributional data presented provides evidence of varying levels (some high) of direct attributability for both common and previously unexplored neuropsychiatric symptoms in SLE. Hallucinations and severe headache were found to be the most directly attributable to SLE. Our data suggest that immunosuppression might prove effective for a diverse range of neuropsychiatric symptoms in some patients and requires further research. This includes those symptoms that are life-changing but rarely specifically targeted for treatment, such as fatigue and cognitive dysfunction. Our findings also highlight that other SARDs may have - currently under-researched and under-estimated - neuropsychiatric symptoms that may be directly attributable to these diseases, and thus the necessity for research into the attribution of NP symptoms in all SARDs.

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## Data sharing statement

Anonymised data will be available on reasonable request following the completion of the INSPIRE studies.

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**Potential conflicts of interest statement**

LA has received consultancy fees/ speaker fees from: Eli Lilly, Glaxo Smith Kline, Janssen, Novartis, UCB, and Werfen Group, CG reports consultancy/advisory fees from: Alumis, Amgen, Astra-Zeneca, Sanofi, UCB and MGP. MSZ declares honoraria for one lecture each from: Norwegian Neurological Society; Copenhagen Neuropsychological Society, Rigshospitalet; Cygnet Healthcare; and UCB Pharma. CW has received speaker fees from UCB. DD'C reports consultancy/speaker fees from GSK, Eli Lilly, Vifor and UCB, and a leadership role on the board of APS support UK. JAB has received speaking fees from Paychiatric Times and Oakstone and receives royalties from American Psychiatric Publishing, Springer International, Lippincott Williams & Wilkins, and Cambridge University Press. All other authors declare no potential conflicts of interest. TP was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the study participants and/or author(s) and not necessarily those of the NHS, the funders, the NIHR or the Department of Health and Social Care.

Table and figure legends:

Table 1 - Limitations of NPSLE attribution literature and how our methods attempted to address these

Table 2 – Participant characteristics

**Table 3– Attributional clues.** Patient and control reported NP symptoms, response to corticosteroids, and relapsing/remitting in conjunction with other disease symptoms (in descending order of rankings of overall direct attributability).

**Fig 1 – Study design flowchart demonstrating the integration of methods at each stage.**

Figure 2 – **Odds ratios of lifetime (experienced >3 times in life) prevalence of neuropsychiatric symptoms among SARDs groups and control participants compared with SLE.** Adjusted models using SLE as the reference (vertical red line). Additional symptom graphs can be found in supplementary information 2, figures A1 and A2.

**Figure 3 A** (Darker and larger boxes signify larger correlations). B Symptom frequency correlations and current disease activity. **(A)** Correlations between frequency of NP symptoms experienced by SLE patients **B)** Correlations of self-assessment of current overall disease activity, pain, fatigue, and validated assessment instrument scores

**Fig 4 –Overall mean rankings for measures of potential direct attributability in SLE for NP symptoms.**

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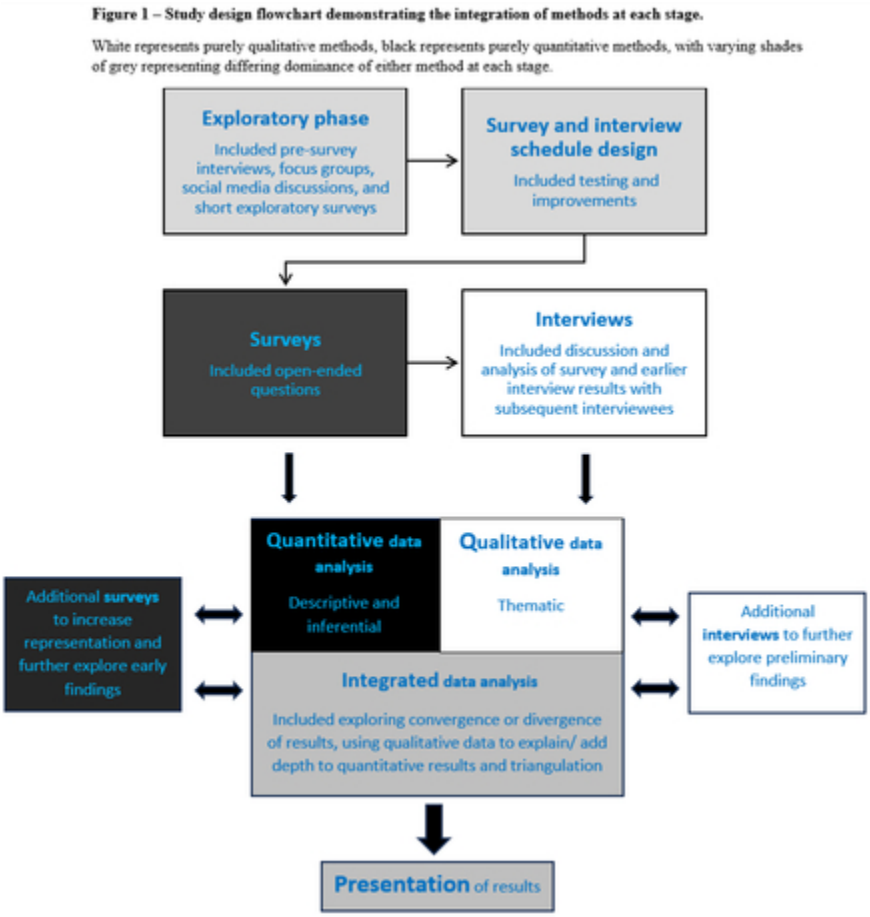
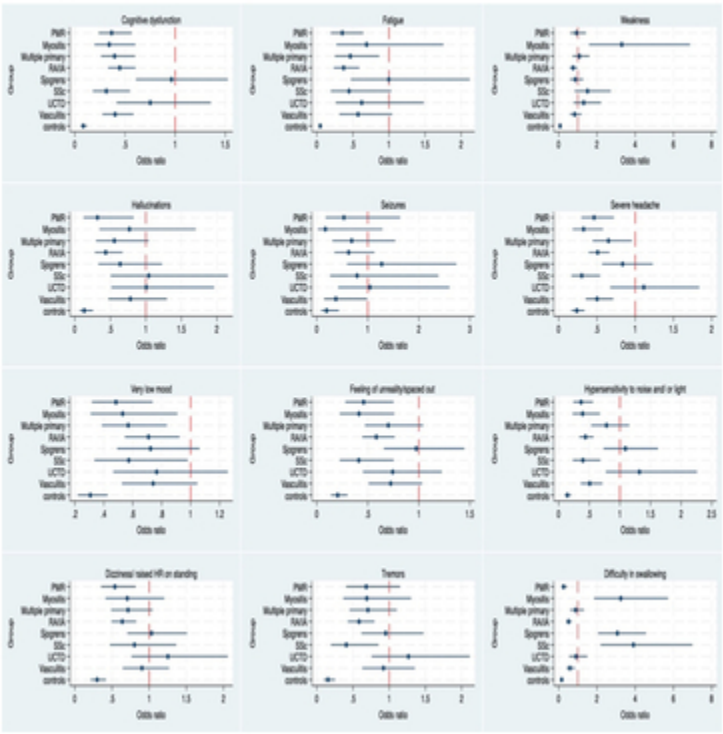



Study design flowchart demonstrating the integration of methods at each stage.

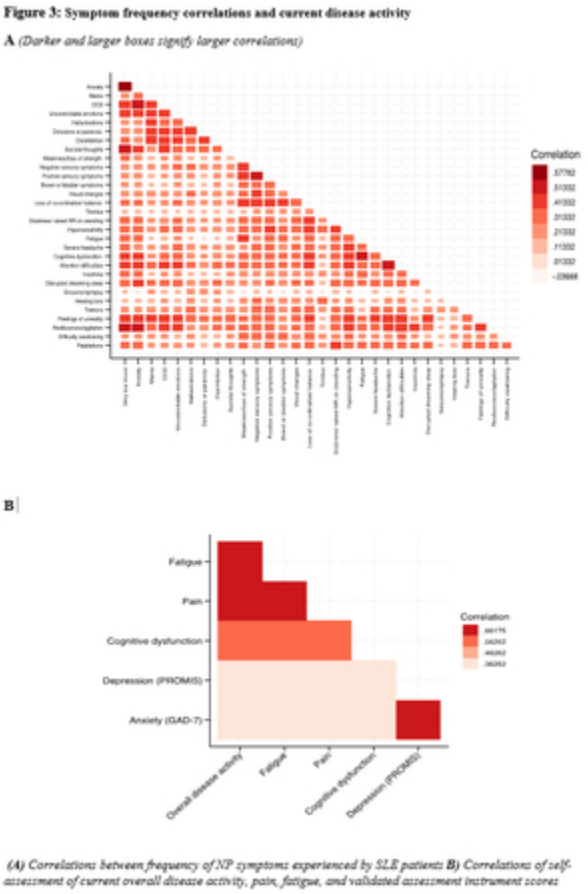
36x38mm (300 x 300 DPI)

**Figure 2 – Odds ratios of lifetime (experienced >3 times in life) prevalence of neuropsychiatric symptoms among SARDs groups and control participants compared with SLE.** Adjusted models using SLE as the reference (vertical red line). Additional symptom graphs can be found in supplementary information 2, figures A1 and A2.




Odds ratios of lifetime (experienced >3 times in life) prevalence of neuropsychiatric symptoms among SARDs groups and control participants compared with SLE. Adjusted models using SLE as the reference (vertical red line). Additional symptom graphs can be found in supplementary information 2, figures A1 and A2.

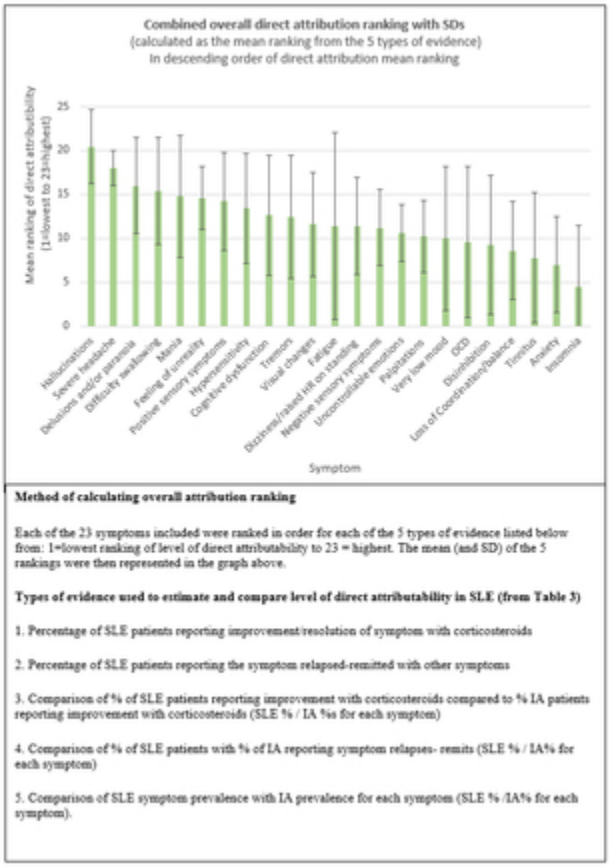
32x36mm (300 x 300 DPI)




A (Darker and larger boxes signify larger correlations). B Symptom frequency correlations and current disease activity. (A) Correlations between frequency of NP symptoms experienced by SLE patients B) Correlations of self-assessment of current overall disease activity, pain, fatigue, and validated assessment instrument scores

25x38mm (300 x 300 DPI)

**Figure 4 –Overall mean rankings for measures of potential direct attributability in SLE for NP symptoms.**




**Method of calculating overall attribution ranking**

Each of the 23 symptoms included were ranked in order for each of the 5 types of evidence listed below from: 1=lowest ranking of level of direct attributability to 23 = highest. The mean (and SD) of the 5 rankings were then represented in the graph above.

**Types of evidence used to estimate and compare level of direct attributability in SLE (from Table 3)**

1. Percentage of SLE patients reporting improvement/resolution of symptom with corticosteroids

2. Percentage of SLE patients reporting the symptom relapsed-remitted with other symptoms

3. Comparison of % of SLE patients reporting improvement with corticosteroids compared to % IA patients reporting improvement with corticosteroids (SLE % / IA %s for each symptom)

4. Comparison of % of SLE patients with % of IA reporting symptom relapses- remits (SLE % / IA% for each symptom)

5. Comparison of SLE symptom prevalence with IA prevalence for each symptom (SLE % /IA% for each symptom).

Overall mean rankings for measures of potential direct attributability in SLE for NP symptoms.

26x38mm (300 x 300 DPI)

Table 1 - Limitations of NPSLE attribution literature and how our methods attempted to address these.

| Evidence for attributing to direct disease effect | Current literature/guidance | Limitations of existing literature | How our study attempts to address existing limitations |
|---|---|---|---|
| Simultaneous presence of other disease activity | *Methods of measuring concurrent disease activity include: Patient records, instruments such as SLEDAI 2k, and clinician judgement of whether a patient is experiencing an SLE flare.* | a. Considerable under-reporting/under-eliciting of NP symptoms and flares [1].<br><br>b. Clinician and patient assessments of whether disease flaring can differ (e.g. subjective symptoms invisible to clinicians)[12].<br><br>c. Timings of routine appointments can be unrelated to disease activity.<br><br>d. Limited clinic time to cover all symptoms[1].<br><br>e. Records/clinician letters often incomplete and inaccurate [24] . | The survey **asks patients directly** when each NP symptom occurs in relation to other flare symptoms (although this is subject to different limitations including recall bias [25], and no availability of confirmatory diagnostic tests) |
| Higher prevalence than in the general population and in other chronic diseases | Most studies restrict symptom inclusion to the original ACR symptom list [10].<br><br>Studies often have no comparison group. | a. Limited number and type of NP symptoms included [10, 26].<br><br>b. Limited/no patient consultation when designing previous symptom lists [10]. Patient symptoms not always directly elicited[1].<br><br>c. Symptoms are sometimes excluded if they are common in general population [11], yet are more prevalent in SLE patients [1], and may be attributable to direct disease process. | **More extensive symptom list** used following patient and clinician input.<br><br>Comparing SLE with controls, and also with IA patients to have a comparison group with a similar burden of chronic disease [5]. |
| Response to immunomodulation treatment | Drug trials often use laboratory and clinician assessment measures to measure treatment response. | a. Patient-reported outcomes measures (PROMS) rarely used as primary outcome measures in clinical trials.<br><br>b. Patients' views can differ from clinician assessments[12].<br><br>c. Diagnostic tests can lack accuracy [3]. | Survey asked patients directly about the response of each NP symptom to corticosteroids (selected over DMARDs due to quicker response to corticosteroids). |
| Timing of first episode of NP symptoms in relation to SLE<br><br>(Note- this data is covered in a separate INSPIRE paper) | *Symptoms considered more likely to result from direct disease effect if they arise within limited time periods around SLE* ***diagnosis*** [2, 27] (although notably Bortoluzzi used timing of disease onset) [28]. | a. Earlier onset NP symptoms often excluded. Diagnostic delays of 6-7 years [29, 30] mean NP symptoms may be an unidentified early part of SLE yet pre-diagnosis NP symptoms often attributed to pre-existing MH disorder [27]. | Timing of other **SLE symptom onset used rather than diagnosis.**<br><br>NP symptom timescales for patients to select from in relation to disease onset included: before, at the same time, and |

| | | | |
|---|---|---|---|
| | | b. Later onset excluded or given less points [28] in attributional model scores. | after (one to four years and ≥5 years). |

**Table 2 – Participant characteristics**

| Characteristic | Patient survey (n=1954) (%) | Patient interviews (n=69) (%) | Control survey (n=463)(%) | Clinician survey (n=400)(%) | Clinician interviews (n=50)(%) |
|---|---|---|---|---|---|
| **Age** | | | | | |
| 18- 30 | 102 (5%) | 6 (9%) | 45 (10%) | 16 (4%) | 0 |
| 30-39 | 209 (11%) | 6 (9%) | 71 (15%) | 135 (34%) | 11 (22%) |
| 40-49 | 325 (17%) | 17 (25%) | 82 (18%) | 135 (34%) | 19 (38%) |
| 50-59 | 546 (28%) | 16 (23%) | 84 (18%) | 69 (17%) | 12 (24%) |
| 60-69 (60+ for clinicians) | 495 (25%) | 10 (13%) | 120 (26%) | 45 (11%) | 8 (16%) |
| 70+ | 274 (14%) | 14 (20%) | 60 (13%) | N/A | N/A |
| Prefer not to say | 3 (<1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) |
| | | | | | |
| **Gender** | | | | | |
| Female | 1749 (90%) | 61 (88%) | 334 (72%) | 209 (52%) | 23 (46%) |
| Male | 197 (10%) | 8 (12%) | 126 (27%) | 186 (47%) | 27 (54%) |
| Other/undisclosed | 8 (<1%) | 0 (0%) | 3 (<1%) | 5 (1%) | 0 (0%) |
| | | | | | |
| **Country/region** | | | | | |
| England | 1368 (70%) | 39 (56%) | 341 (74%) | 156 (39%) | 28 (56%) |
| Scotland | 147 (8%) | 7 (10%) | 43 (9%) | 16 (4%) | 2 (4%) |
| Wales | 104 (5%) | 7 (10%) | 20 (4%) | 6 (2%) | 2 (4%) |
| N. Ireland or Republic of Ireland | 35 (2%) | 3 (4%) | 7 (2%) | 2 (<1%) | 0 (0%) |
| US or Canada | 117 (6%) | 4 (6%) | 16 (3%) | 65 (16%) | 4 (8%) |
| Europe | 126 (6%) | 4 (6%) | 24 (5%) | 68 (17%) | 6 (12%) |
| Asia | 21 (1%) | 2 (3%) | 1 (<1%) | 34 (9%) | 3 (6%) |
| Latin America | 4 (<1%) | 0 (0%) | 2 (<1%) | 30 (8%) | 4 (8%) |
| Australia or New Zealand | 19 (1%) | 2 (3%) | 0 (0%) | 10 (3%) | 0 (0%) |
| Other | 13 (<1%) | 1 (1%) | 9 (2%) | 13 (3%) | 1 (2%) |
| | | | | | |
| **Ethnicity** | | | | Not recorded | Not recorded |
| White | 1746 (89%) | 56 (81%) | 434 (95%) | | |
| Asian | 77 (4%) | 7 (10%) | 6 (1%) | | |
| Black | 41 (2%) | 4 (6%) | 4 (1%) | | |
| Mixed | 53 (3%) | 2 (3%) | 11 (2%) | | |
| Other | 19 (1%) | 0 (0%) | 2 (<1%) | | |
| Undisclosed | 18 (1%) | | | | |
| | | | | | |
| **Disease** | | | N/A | N/A | N/A |
| SLE | 609 (31%) | 27 (39%) | | | |
| Inflammatory arthritis | 489 (25%) | 9 (13%) | | | |
| Vasculitis | 209 (11%) | 3 (4%) | | | |
| Sjögren's | 152 (8%) | 6 (9%) | | | |
| PMR | 132 (7%) | 7 (10%) | | | |
| UCTD | 77 (4%) | 9 (13%) | | | |
| Myositis | 64 (3%) | 3 (4%) | | | |
| Systemic sclerosis | 67 (3%) | 2 (3%) | | | |
| Mixed/multiple | 143 (7%) | 3 (4%) | | | |
| | | | | | |
| **Clinician Role** | N/A | N/A | N/A | | |
| Rheumatologist | | | | 204 (51%) | 20 (40%) |
| Psychiatrist | | | | 96 (24%) | 8 (16%) |
| Neurologist | | | | 52 (13%) | 10 (20%) |
| Rheumatology nurse | | | | 20 (5%) | 4 (8%) |
| GP/Primary care | | | | 11 (3%) | 5 (10%) |

| | | | | | |
|---|---|---|---|---|---|
| Other | | | | 27 (7%) | 3 (6%) |

**Table 3– Attributional clues.** Patient and control reported NP symptoms, response to corticosteroids, and relapsing/remitting in conjunction with other disease symptoms (in descending order of rankings of overall direct attributability).

| | **Column 1 Lifetime prevalence % of each group reporting having experienced the symptom >3 times in their lives** | | | | **Column 2 % of patients reporting symptom improved/resolved on corticosteroids**** | | | **Column 3 % of patients reporting symptom relapses/remits with other symptoms**** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Controls N=418 % | SLE N=548 % | RA/IA N=450 % | p value* ($Chi^2$) | SLE % | RA/IA % | p value ($Chi^2$) | SLE % | RA/IA % | p value ($Chi^2$) |
| **Hallucinations** | 4 | 15 | 7 | **<0.001** | 59 | 27 | **0.047** | 45 | 21 | **0.039** |
| **Severe headache** | 23 | 59 | 40 | **<0.001** | 51 | 30 | **0.008** | 60 | 36 | **<0.001** |
| **Delusions and/or paranoia** | 5 | 11 | 7 | **0.044** | 36 | 23 | 0.396 | 42 | 18 | 0.064 |
| **Difficulty swallowing** | 9 | 39 | 25 | **<0.001** | 43 | 21 | **0.025** | 37 | 27 | 0.118 |
| **Mania** | 8 | 20 | 13 | **<0.001** | 35 | 21 | 0.243 | 33 | 14 | **0.023** |
| **Feeling of unreality** | 15 | 47 | 32 | **<0.001** | 52 | 32 | **0.021** | 44 | 34 | 0.084 |
| **Positive sensory symptoms** | 20 | 63 | 47 | **<0.001** | 53 | 43 | 0.171 | 56 | 54 | 0.558 |
| **Hypersensitivity to noise and/or light** | 18 | 67 | 44 | **<0.001** | 24 | 17 | 0.244 | 53 | 40 | **0.013** |
| **Cognitive dysfunction** | 22 | 82 | 66 | **<0.001** | 47 | 36 | 0.100 | 66 | 66 | 0.927 |
| **Tremors** | 7 | 30 | 18 | **<0.001** | 35 | 33 | 0.899 | 44 | 28 | **0.033** |
| **Visual changes** | 9 | 36 | 27 | **0.004** | 32 | 16 | 0.071 | 35 | 27 | 0.217 |
| **Fatigue** | 34 | 94 | 86 | **<0.001** | 66 | 70 | 0.408 | 79 | 86 | 0.041 |
| **Dizziness/raised HR on standing** | 28 | 56 | 44 | **<0.001** | 39 | 21 | **0.010** | 41 | 40 | 0.762 |
| **Negative sensory symptoms** | 8 | 38 | 29 | **0.001** | 43 | 40 | 0.768 | 47 | 46 | 0.858 |
| **Uncontrollable emotions** | 14 | 39 | 26 | **<0.001** | 34 | 33 | 0.879 | 43 | 34 | 0.176 |
| **Palpitations** | 27 | 62 | 48 | **<0.001** | 27 | 18 | 0.177 | 40 | 28 | **0.024** |
| **Very low mood** | 35 | 67 | 55 | **<0.001** | 41 | 46 | 0.507 | 70 | 73 | 0.522 |
| **OCD** | 17 | 36 | 23 | **<0.001** | 26 | 31 | 0.619 | 33 | 19 | **0.030** |
| **Disinhibition** | 9 | 18 | 13 | 0.054 | 24 | 21 | 0.835 | 27 | 15 | 0.128 |
| **Loss of coordination/ balance** | 14 | 57 | 49 | **0.008** | 28 | 30 | 0.745 | 54 | 51 | 0.563 |
| **Tinnitus** | 28 | 47 | 46 | 0.567 | 27 | 16 | 0.109 | 33 | 25 | 0.134 |
| **Anxiety** | 41 | 68 | 56 | **<0.001** | 30 | 37 | 0.326 | 54 | 56 | 0.694 |
| **Insomnia** | 49 | 79 | 75 | 0.131 | 20 | 28 | 0.115 | 54 | 61 | 0.118 |

Symptoms are listed in descending order of overall SLE rankings of attributability

* P values for all columns are from comparing SLE and RA/IA symptom lifetime prevalences. P values between Controls and SLE for column 1 are all p<0.001.

** Numbers for column 2 and 3 ranged from n=4 (RA) and n=15 (SLE) for delusions to n=230 (RA) and 285 (SLE) for fatigue. Denominators= % of patients in that disease group who had experienced that symptom >3

times (and had received steroids for column 2 or reported a generally relapsing/remitting disease course for column 3)

# Consistent safety profile with over 8 years of real-world evidence, across licensed indications[1–3]

Cosentyx® secukinumab

**1,000,000** patients treated globally, and counting*[4]

**100+** clinical trials*[5]

**8+ years** of real-world evidence[1–3]

**8** indications[1–3]

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## Real-world evidence shows a consistent safety profile over 6 years[6,7]

No trend toward increased AE rates over time (pooled PsA, AS, PsO):†[6]

| AEs of select interest (EAIR per 100 PY) | 1 year | 2 years | 3 years | 4 years | 5 years | 6 years | Cumulative rate |
|---|---|---|---|---|---|---|---|
| Serious infections Cases | 2.0 n=149 | 1.7 n=475 | 0.7 n=649 | 1.3 n=1,841 | 1.3 n=2,285 | 1.1 n=2,226 | 1.3 n=8,719 |
| Malignant or unspecified tumours Cases | 0.2 n=15 | 0.2 n=50 | 0.2 n=225 | 0.3 n=422 | 0.3 n=520 | 0.3 n=573 | 0.3 n=1,896 |
| MACE Cases | 0.2 n=15 | 0.1 n=39 | 0.2 n=151 | 0.2 n=238 | 0.2 n=264 | 0.1 n=287 | 0.2 n=1,031 |
| Total IBD Cases | 0.2 n=12 | 0.2 n=46 | 0.2 n=185 | 0.3 n=340 | 0.2 n=312 | 0.1 n=261 | 0.2 n=1,291 |
| Exposure (PY) | 7450 | 28,549 | 93,744 | 137,325 | 182,024 | 212,636 | 680,470 |

**No trend towards increased rates of malignancy, MACE or IBD over time[6]**

**The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[1,2] Refer to the prescribing information for a summary of adverse events.**

Adapted from Novartis Data on File. 2021.[6]

**Refer to the Cosentyx Summary of Product Characteristics for full details, dosing and administration, including special populations.**

**Cosentyx® (secukinumab) licensed indications in rheumatology:** Cosentyx, alone or in combination with methotrexate, is indicated for the treatment of active **psoriatic arthritis** in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active **ankylosing spondylitis** in adults who have responded inadequately to conventional therapy; active **non-radiographic axial spondyloarthritis** with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active **enthesitis-related arthritis** in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active **juvenile psoriatic arthritis** in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[1,2]

**Prescribing information, adverse event reporting and full indication can be found on the next page.**

*Patients prescribed Cosentyx for any indication since launch.

†Successive time periods of PSUR shown with cumulative rate: 26 Dec 2014 to 25 Dec 2015; 26 Dec 2015 to 25 Dec 2016; 26 Dec 2016 to 25 Dec 2017; 26 Dec 2017 to 25 Dec 2018: 26 Dec 2018 to 25 Dec 2019; 26 Dec 2019 to 25 Dec 2020.[6]

**Abbreviations:** AE, adverse event; AS, ankylosing spondylitis; EIAR, exposure-adjusted incidence rate; HCP, healthcare professional; IBD, inflammatory bowel disease; MACE, major adverse cardiac event; PsA, psoriatic arthritis; PsO, plaque psoriasis; PY, patient year.

**References: 1.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **2.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **3.** European Medicines Agency. European public assessment report. Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed February 2024]; **4.** Novartis Data on File. Secukinumab – Sec008. 2023; **5.** Novartis. Novartis Cosentyx® positive 16-week PREVENT results advance potential new indication for patients with axial spondyloarthritis. Available at: https://www.novartis.com/news/media-releases/novartis-cosentyx-positive-16-week-prevent-results-advance-potential-new-indication-patients-axial-spondyloarthritis [Accessed February 2024]; **6.** Novartis data on file. Cosentyx Periodic Safety Update Report (PSUR); 26 December 2019 – 25 December 2020. 22 February 2021; **7.** Deodhar A, et al. Arthritis Res Ther 2019;21(1):111.

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UK | February 2024 | 407722

## Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

### Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

**Indications:** Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000):* anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

**UK | 284832 | May 2023**

**Adverse Event Reporting:**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

## Cosentyx® (secukinumab) Great Britain Prescribing Information.

### Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

**Indications:** Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions*: Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

**UK | 290802 | June 2023**

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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com