# Clinical phenotypes, classification, and long-term outcomes of childhood-onset Sjögren's disease into adulthood: a single-centre cohort study

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## Summary

**Background** Childhood-onset Sjögren's disease is a rare and under-investigated rheumatic condition. The natural course of childhood-onset Sjögren's disease in adulthood in not known. This study aimed to evaluate long-term disease trajectories and complications of childhood-onset Sjögren's disease and explore management strategies.

**Methods** This combined retrospective and prospective analysis of a childhood-onset Sjögren's disease cohort with long-term follow-up into adulthood was done in individuals aged 13–36 years with childhood-onset Sjögren's disease recruited from a single tertiary adolescent and young adult rheumatology service at University College London Hospital, UK. Participants were either approached consecutively during routine clinical appointments, or their data were collected retrospectively from the time of diagnosis to the time of transition to the service, and prospectively thereafter. We mapped the cohort onto clinical phenotypes defined by the Florida Scoring System at disease onset and stratified them based on the Newcastle Sjögren's Stratification Tool at last assessment. Disease activity, symptom severity, and damage trajectories were assessed using European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), and Sjögren's Syndrome Disease Damage Index (SSDDI), respectively. People with related lived experience were involved in the study design and implementation.

**Findings** Between March 1, 2020, and June 30, 2024, we identified 30 children and young people diagnosed with childhood-onset Sjögren's disease based on expert opinion. Mean age at onset was 12·7 years (SD 3·3). 28 (93%) of 30 individuals were female and two (7%) were male. The most common disease manifestations at onset were fatigue (22 [73%] of 30 individuals), arthralgia (21 [70%]), dryness (17 [57%]), glandular swelling (15 [50%]), and skin rashes (ten [30%]). Diagnostic delay of more than 3 years from symptoms onset increased the prevalence of reported dryness (nine [100%] of nine *vs* eight [38%] of 21; p=0·0014). Children and young people with childhood-onset Sjögren's disease had two distinct disease activity and symptom trajectories (high ESSDAI: mean 3·9 [SD 2·2] *vs* low ESSDAI: mean 0·8 [1·1]; p<0·0001 and high ESSPRI: mean 5·6 [2·7] *vs* low ESSPRI: mean 3·1 [1·0]; p=0·036), which could not be predicted by sex or age at onset, symptom duration, or duration of follow-up. Damage accrual did not differ based on activity and symptom trajectory (p=0·080 and p=1·0, respectively). At last review, the median ESSDAI score was 2·0 (IQR 2·0–8·0) and the ESSPRI score was 5·3 (3·0–7·0). Four (13%) of 30 patients developed lymphoma and 17 (57%) accumulated damage (SSDDI score ≥1).

**Interpretation** This preliminary evaluation of long-term outcomes of childhood-onset Sjögren's disease in adulthood showed distinct patterns of disease and symptom trajectories and that a high proportion of children and young people develop damage in early adulthood. These findings highlight the need for improved research quality and evidence-based management strategies for better outcomes in this population.

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## Introduction

Childhood onset Sjögren's disease is a rare clinical phenotype without robust clinical and immunological characterisation or assessment of its impact on quality of life. These aspects hamper progress in the management and delivery of high-quality research and evidence-based recommendations for care.[1] Despite efforts to propose and validate age-specific diagnostic algorithms and criteria,[2–4] evaluate the performance of adult Sjögren's disease classification criteria,[5] and extrapolate management strategies from adult Sjögren's disease,[6,7] there are no publications following up children and young people (ie, aged <18 years) with childhood-onset Sjögren's disease into adulthood. Consequently, the natural course of childhood-onset Sjögren's disease is not known. The possible differences in disease phenotypes according to

## Research in context

### Evidence before this study

Childhood-onset Sjögren's disease is an orphan rheumatic condition, which is under-recognised and under-diagnosed. In 2022, we performed and published a systematic review of the literature that included suitable reports highlighting pharmacological treatment of childhood-onset Sjögren's disease, which were identified using PubMed and EMBASE database searches from database inception to December, 2020. Search terms were "juvenile Sjögren's syndrome" OR "childhood onset Sjogren's syndrome" OR "Sjogren's syndrome with childhood onset" OR "Sjögren's syndrome in children" OR "paediatric Sjögren's syndrome" OR "recurrent parotitis" OR "sicca in children". We completed another systematic review of the literature published up to Aug 31, 2025, using similar search terms, as part of an international initiative to develop paediatric specific classification criteria, and no childhood-onset Sjögren's disease studies with long-term follow-up into adulthood were identified.

### Added value of this study

To our knowledge, this is the first study evaluating the natural course of childhood-onset Sjögren's disease into adulthood, including cumulative clinical manifestations mapped against the available diagnostic and classification criteria and diagnostic algorithms, adult-validated disease activity and damage assessment tools, and patient-reported outcomes. The study showed the disease course over a median of 10 years in a single-centre childhood-onset Sjögren's disease cohort with up to 25 years of follow-up. Disease activity and symptoms trajectories over time revealed two distinct groups. These findings have important implications for exploring the heterogeneity of this condition and prevalence of severe manifestations, including lymphoma, over time. It also emphasises the severity of childhood-onset Sjögren's disease in adulthood, highlighting gaps in current knowledge and the needs for better research to inform future policies.

### Implications of all the available evidence

This study highlights the need to define the natural course of this rare paediatric rheumatic condition in larger, diverse cohorts. Further research is needed to ascertain whether the early damage accrual, high rate of lymphoma, and disease activity and symptom burden phenotypes observed can be widely validated and to identify the best management strategies to minimise the risk of poor outcomes later in life.

age at disease onset cannot be fully understood because of the absence of harmonised cohort registries across the life span and scarcity of linked paediatric and adult clinical rheumatology services.

Children and young people and their families face the challenge of delayed diagnosis because this rare condition is not recognised,[1] and for many years it has been described as affecting only adults. The diagnosis and management of children and young people is based on expert opinion alone or informed by extrapolation of the management strategies available for adult Sjögren's disease[7,8] since good quality research in paediatric populations is scarce. Proposals for diagnostic algorithms[2,9] and classification strategies for childhood-onset Sjögren's disease[3] have marked noteworthy progress, highlighting the investment of the paediatric community in raising awareness and educating and supporting multidisciplinary teams to ensure timely disease diagnosis. However, these proposals still require further validation in ethnically and geographically diverse cohorts to support wider clinical implementation. Clinicians and scientists cannot answer important questions about the similarities and differences between individuals diagnosed with Sjögren's disease in childhood versus adulthood since data on long-term activity or damage trajectories are absent and the life-long risk of lymphoma, which is estimated to be 4–14% in adult Sjögren's disease,[10,11] is not known in childhood-onset Sjögren's disease. Another major challenge in characterising childhood-onset Sjögren's disease is the absence of validated paediatric outcome measures,[12] which hamper the objective assessment of disease activity or the evaluation of the subjective impact of symptoms. There are no validated patient-reported outcome measures for childhood-onset Sjögren's disease, which affects direct comparisons between the phenotype of childhood-onset Sjögren's disease and that of adult disease.

This study aimed to evaluate, within the limitations of data available in clinical practice and the disease rarity, the long-term outcomes of childhood-onset Sjögren's disease followed up to adulthood. This study has been conducted retrospectively and prospectively, thus making use of the diagnostic and classification tools available for paediatric and adult populations and objectively assessing the disease outcomes and therapeutic approaches used over time. Additionally, we evaluated the risk and outcomes of lymphoma as the prevalence of this complication in adulthood is unknown since most studies on childhood-onset Sjögren's disease have been conducted in paediatric services and have shorter follow-up.

## Methods

### Study design and participants

We performed a combined retrospective and prospective longitudinal analysis of an adolescent cohort of childhood-onset Sjögren's disease with long-term follow-up. Individuals were recruited from a single tertiary adolescent and young adult rheumatology service at University College London Hospital, UK. There were no specific referral criteria for this cohort, and all individuals were diagnosed based on expert opinion. Every child or young

person (aged 13–17 years) who transitioned from a paediatric service with a diagnosis of childhood-onset Sjögren's disease was enrolled and accepted under our care. We also evaluated all newly referred individuals for suspected childhood-onset Sjögren's disease and included only those diagnosed with probable or definite childhood-onset Sjögren's disease based on expert opinion (including multidisciplinary team assessments and discussions).

This study was approved by the London-Harrow Research Ethics Committee (reference 11/LO/0330). Written informed parental consent or participant assent or consent, as developmentally and age-appropriate, was collected when they joined the adolescent rheumatology service, with permission for use of retrospective data. We involved people with related lived experience in the study design and implementation (prior to REC approval) and plan to involve them further in the results dissemination.

All potential participants were approached in a consecutive manner during routine clinical appointments to minimise selection bias. Participants were recruited between March 1, 2020, and June 30, 2024, and followed up at regular intervals of 6 months or more frequently as per clinical need.

For individuals diagnosed with childhood-onset Sjögren's disease before joining the adolescent rheumatology service, we collected data retrospectively from the time of diagnosis to the time of transition to the service, and prospectively afterwards. Many individuals diagnosed in childhood transitioned from Great Ormond Street Hospital in London, and data collection was facilitated by joined Electronic Health Records between the two hospitals (the EPIC system). We reported sex and/or gender and ethnicity as per NHS categories. In this cohort, sex and gender was congruent.

### Procedures

To evaluate differences in clinical phenotypes, we mapped the cohort of childhood-onset Sjögren's disease onto the clinical phenotypes defined by the Florida Scoring System[3] at disease onset (as these criteria are only suitable to apply at presentation) and stratified them based on the Newcastle Sjögren's Stratification Tool validated in adult Sjögren's disease[13] at last assessment. The Florida Scoring System is an instrument derived from a younger cohort presenting to dentists and oral medicine specialists in the USA.[14] The Newcastle Sjögren's Stratification Tool comprised European Alliance of Associations for Rheumatology (EULAR) Sjögren's Syndrome Patient Reported Index (ESSPRI)-dryness (scale of 0–10), ESSPRI-fatigue (0–10), and ESSPRI-pain (0–10), and Hospital Anxiety and Depression Scale (HADS)-anxiety (0–21) and HADS-depression (0–21).[15] Data on anxiety and depression were not available when individuals were assessed at presentation to the paediatric service as HADS is not a suitable tool and routine assessment of depression and anxiety in children is not part of routine practice.

We evaluated glandular imaging and biopsy features based on validated outcome measures used in adults: the Outcome Measures in Rheumatology (OMERACT) scoring system for ultrasound assessment in adult Sjögren's disease[16] and the presence of lymphocytic sialadenitis with a positive focus score of 1 or higher. We also characterised the therapeutic strategies used for glandular and extra-glandular manifestations at disease onset throughout the disease course and cumulatively at last assessment.

All individuals were evaluated by oral medicine specialists (regarding the added value of having a minor salivary gland biopsy in the context of clinical presentation) for serology, probability of childhood-onset Sjögren's disease diagnosis, and effect of biopsy on management.

### Procedures and outcomes

We characterised the natural history of childhood-onset Sjögren's disease, including clinical manifestations, serological features, and treatments at first appointment in paediatric or adolescent rheumatology services as per age at referral. We also collected similar data for subcohorts at 1, 5, 10, and 15 years post-diagnosis and assessed the cumulative disease features and therapeutic exposures at the last clinical assessment for the whole childhood-onset Sjögren's disease cohort.

We assessed disease activity, symptom severity, and damage trajectories using validated scores available for adult disease (EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI], ESSPRI, and Sjögren's Syndrome Disease Damage Index [SSDDI], respectively,[12] at disease onset, follow-up, and last assessment).

We also established the proportion (positivity rate) of individuals with childhood-onset Sjögren's disease who fulfilled proposed paediatric diagnosis criteria,[2,4] as well as the 2016 American College of Rheumatology (ACR)–EULAR adult Sjögren's disease classification criteria[17] at presentation and the last assessment. There is currently no gold standard for diagnosis or classification of childhood-onset Sjögren's disease.

### Statistical analysis

We used descriptive statistics to assess demographics and clinical and serological features. We evaluated disease activity and symptom trajectory over time using latent class growth analysis to identify distinct subgroups based on their longitudinal ESSDAI and ESSPRI profiles. Latent class growth analysis was performed in R (version 4.4.3) using the lcmm package.[18] Specifically, we used the hlme function to fit models with one to four latent classes. For two-class to four-class model, we used the gridsearch function with 30 random starts for each model, using the one-class model as the baseline (minit). Model selection was guided by the Bayesian Information Criterion and Akaike Information Criterion, with the lower values indicating a better fit

| | At diagnosis (n=30) | At last assessment (n=30)* |
|---|---|---|
| Age, years | 12·7 (3·3) | 25·8 (5·2) |
| Duration of symptoms, years | 1 (1–3) | 12 (10–15) |
| Sex | | |
| Male | 2 (7%) | 2 (7%) |
| Female | 28 (93%) | 28 (93%) |
| Race | | |
| Asian | 6 (20%) | 6 (20%) |
| Black | 7 (23%) | 7 (23%) |
| White | 17 (57%) | 17 (57%) |
| Classification and phenotype assessment | | |
| Diagnostic and classification criteria fulfilled | | |
| 2016 ACR–EULAR criteria | 12 (40%) | 20 (67%) |
| Paediatric diagnostic criteria[4] | 9 (30%) | 14 (47%) |
| Definite or probable diagnosis[2] | 12 (40%) | 19 (63%) |
| Probable or childhood-onset Sjögren's disease diagnosis[9] | 21 (70%) | 27 (90%) |
| Mapping onto paediatric FSS-derived categories at diagnosis[3]† | | |
| Dryness with positive tests | 8 (27%) | Not applicable |
| High symptoms with negative tests | 5 (17%) | Not applicable |
| Low symptoms with negative tests | 1 (3%) | Not applicable |
| Unclassifiable§ | 17 (57%) | Not applicable |
| Mapping onto NSST-derived adult clinical phenotypes[14]‡ | | |
| High symptom burden | Not available | 11 (37%) |
| Low symptom burden | Not available | 9 (30%) |
| Pain dominant with fatigue | Not available | 8 (27%) |
| Dryness dominant with fatigue | Not available | 2 (7%) |

ACR=American College of Rheumatology. EULAR=European Alliance of Associations for Rheumatology. FSS=Florida Scoring System. NSST=Newcastle Sjögren's Stratification Tool. *All individuals aged 18 years or older. †Not applicable to the last assessment as FSS is defined as a diagnostic tool for use at disease presentation to dentists or oral medicine specialists. ‡Data not available at diagnosis as many individuals were diagnosed in the paediatric service (data collected retrospectively) and Hospital Anxiety and Depression Scale is not suitable for use in children. §Unclassifiable as presented with high or low symptoms but had positive tests.

***Table 1:*** **Demographics, classification, and diagnostic criteria at presentation versus last assessment**

(which in the case of these data was achieved with a two-class model).

Group comparisons were conducted using the Mann–Whitney U test for continuous variables. The result of a hypothesis test was deemed statistically significant if the p value was less than 0·05. Missing data were assessed for pattern and extent. A latent class growth sub-analysis was performed on the subset of participants for whom complete ESSPRI data were available at least at four different timepoints. This approach allowed for targeted evaluation of ESSPRI trajectory, while minimising bias introduced by imputation.

### Role of the funding source

There was no funding source for this study.

## Results

Between March 1, 2020, and June 30, 2024, 30 children and young people diagnosed with probable or definite childhood-onset Sjögren's disease were assessed for eligibility and enrolled. Individuals were followed up for a mean of 10 years (SD 5·4) post-diagnosis, and up to a maximum of 25 years. One potential participant declined inclusion when approached and one withdrew consent for ongoing follow-up data collection, both due to personal preference. 28 (93%) of 30 individuals were female and two (7%) were male (table 1). Mean age at onset was 12·7 years (SD 3·3).

All individuals were diagnosed with childhood-onset Sjögren disease based on expert opinion.[4,12] A minor salivary gland biopsy was discussed and offered to 20 (67%) of 30 individuals with childhood-onset Sjögren disease. For the remaining ten individuals (with clinical features of childhood-onset Sjögren disease, positive serology, and relevant salivary glandular ultrasound findings), a biopsy was considered to have no added value for diagnosis or management and, therefore, was not recommended.

After exploring risks and benefits for having a minor salivary gland biopsy with each individual and their carers or family, 15 (75%) of 20 individuals agreed to have a biopsy, of whom 12 (40% of the whole cohort) had a diagnostic result (ie, focus score of ≥1, defined as >50 lymphocytic cell infiltrations in 4 mm²). Three individuals had non-diagnostic biopsies (lymphocytic infiltration but a focus score <1).

When we assessed the performance of the available paediatric diagnostic algorithm[2] and criteria[4] and the 2016 ACR–EULAR adult Sjögren's disease classification criteria[17] at diagnosis and last assessment, most individuals with childhood-onset Sjögren's disease (nine [29%] of 31 at baseline and 12 [39%]) of 31 at diagnosis) could not be diagnosed or classified using these tools (table 1). Data were available for all participants. The clinical phenotype of individuals with childhood-onset Sjögren's disease at diagnosis was not captured by the distinct clusters defined by Florida Scoring System for childhood-onset Sjögren's disease,[3] highlighting differences in symptom duration and disease presentation across distinct health-care services or medical specialties, in addition to possible geographical differences. When we stratified the cohort using the Newcastle Sjögren's Stratification Tool, there was a higher proportion of individuals with high symptom burden, but a lower proportion with dryness dominance with fatigue, than in individuals in adult studies.[13] These findings suggest that adults with childhood-onset Sjögren's disease might have distinct clinical phenotypes compared with adult Sjögren's disease (table 1), with the caveat of the small sample size.

The main reason for the increased proportion of individuals fulfilling various criteria over time was that more children and young people developed objective dryness (from 17 [57%] of 30 at baseline to 23 [77%] cumulatively; table 2), in addition to suggestive imaging features of sialadenitis on ultrasound examination over time. Therefore, the proportion of individuals fulfilling various criteria increased by approximately 20% over the duration of follow-up. Only one individual had a repeated

biopsy (diagnostic after a previous non-conclusive biopsy) and was, therefore, diagnosed with childhood-onset Sjögren's disease.

The most common overlapping phenotypes with childhood-onset Sjögren's disease were childhood-onset systemic lupus erythematosus (SLE; diagnosed in

| | Disease onset (n=30) | 1-year follow-up (n=30) | 5-year follow-up (n=27) | 10-year follow-up (n=19) | 15-year follow-up (n=5) | Cumulatively at last review (n=30) |
|---|---|---|---|---|---|---|
| **Clinical manifestations** | | | | | | |
| Extra-glandular manifestations and biological activity | | | | | | |
| Fatigue | 22 (73%) | 22 (73%) | 22 (81%) | 14 (74%) | 5 (100%) | 30 (100%) |
| Arthralgia | 21 (70%) | 21 (70%) | 18 (67%) | 10 (53%) | 2 (40%) | 27 (90%) |
| Skin rashes | 10 (33%) | 10 (33%) | 7 (26%) | 3 (16%) | .. | 10 (33%) |
| Skin vasculitis | 1 (3%) | 2 (7%) | 1 (4%) | 0 | 0 | 3 (10%) |
| Increased IgG | 10 (33%) | 10 (33%) | 8 (30%) | 6 (32%) | 2 (40%) | 12 (40%) |
| Lymphadenopathy | 10 (33%) | 5 (17%) | 5 (19%) | 6 (32%) | - | 10 (33%) |
| Increased amylase* | 7/20 (35%) | 10/27 (37%) | 12/28 (43%) | 5/19 (26%) | 1/5 (20%) | 12/30 (40%) |
| Constitutional symptoms | 5 (17%) | 4 (13%) | 4 (15%) | 2 (11%) | .. | 7 (23%) |
| Cytopenia | 5 (17%) | 5 (17%) | 4 (15%) | 3 (16%) | .. | 5 (17%) |
| Arthritis | 2 (7%) | 2 (7%) | 2 (7%) | 3 (16%) | .. | 3 (10%) |
| Gastrointestinal symptoms | 2 (7%) | 4 (13%) | 3 (11%) | 3 (16%) | .. | 5 (17%) |
| Myositis | 1 (3%) | 1 (3%) | 2 (7%) | - | .. | 2 (7%) |
| Renal involvement | .. | 1 (3%) | 2 (7%) | - | .. | 3 (10%) |
| Pulmonary involvement (interstitial lung disease or bronchiectasis) | .. | 1 (3%) | 1 (4%) | 2 (11%) | .. | 2 (7%) |
| Peripheral T-cell lymphoma | .. | .. | 1 (4%) | | .. | 1 (3%) |
| Recurrent optic neuritis and transverse myelitis (CNS involvement) | .. | .. | 1 (4%) | 1 (5%) | 1 (20%) | 1 (3%) |
| Seizures (CNS involvement) | .. | .. | .. | 1 (5%) | .. | 1 (3%) |
| Dysautonomia | .. | .. | .. | 2 (11%) | 2 (40%) | 2 (7%) |
| Glandular manifestations | | | | | | |
| Dryness | 17 (57%) | 18 (60%) | 18 (67%) | 13 (68%) | 5 (100%) | 23 (77%) |
| Glandular swelling | 15 (50%) | 11 (37%) | 7 (26%) | 5 (26%) | 1 (20%) | 15 (50%) |
| MALT lymphoma | 1 (3%) | .. | .. | 1 (5%) | 1 (20%) | 3 (10%) |
| **Treatments used** | | | | | | |
| For extra-glandular manifestations | | | | | | |
| Hydroxychloroquine† | 11 (37%) | 25 (83%) | 25 (93%) | 17 (89%) | 5 (100%) | 25 (83%) |
| Methotrexate | 2 (7%) | 2 (7%) | 6 (22%) | 4 (21%) | .. | 7 (23%) |
| Azathioprine | 2 (7%) | 7 (23%) | 9 (33%) | 5 (26%) | .. | 11 (37%) |
| Intravenous methylprednisolone | 1 (3%) | 3 (10%) | 6 (22%) | 3 (16%) | 1 (20%) | .. |
| Mycophenolate mofetil | .. | 4 (13%) | 8 (30%) | 4 (21%) | 1 (20%) | 8 (27%) |
| Cyclophosphamide | .. | 2 (7%) | .. | .. | - | 3 (10%) |
| Rituximab | .. | 2 (7%) | 3 (11%) | 1 (5%) | 1 (20%) | 5 (17%) |
| Adalimumab | .. | 1 (3%) | .. | .. | .. | 1 (3%) |
| Belimumab and mycophenolate mofetil | .. | .. | 1 (4%) | 1 (5%) | .. | 1 (3%) |
| Cyclophosphamide and rituximab | .. | .. | 1 (4%) | .. | .. | .. |
| Baricitinib | .. | .. | .. | 1 (5%) | .. | 1 (3%) |
| For glandular manifestations | | | | | | |
| NSAIDs | 22 (73%) | 10 (33%) | 7 (26%) | .. | .. | 22 (73%) |
| Short course of prednisolone | 8 (27%) | 4 (13%) | 4 (15%) | .. | .. | 8 (27%) |
| Pilocarpine | .. | 1 (3%) | 7 (26%) | 6 (32%) | 1 (20%) | 8 (27%) |
| Methylprednisolone washouts | .. | .. | .. | 2 (11%) | .. | 4 (13%) |
| Rituximab | .. | .. | .. | 1 (5%) | .. | 2 (7%) |

Data are n (%) or n/N (%). MALT=mucosal-associated lymphoid tissue. NSAIDs=non-steroidal anti-inflammatory drugs. *Out of the number tested. †In many individuals, treatment with hydroxychloroquine was given for glandular and extra-glandular manifestations.

***Table 2:*** **Childhood-onset Sjögren's disease manifestations and treatment during disease course and cumulatively at last assessment**

seven [23%] of 30 individuals) and juvenile idiopathic arthritis (diagnosed in two [7%] of 30). These diagnoses occurred before that of childhood-onset Sjögren's disease, with the exception of one individual diagnosed with childhood-onset SLE and childhood-onset Sjögren's disease at the same time, and four (13%) who were initially diagnosed with undifferentiated connective tissue disease. Two individuals had additional symptoms and positive serology for coeliac disease and two had hypothyroidism requiring treatment with levothyroxine. Data were available for all participants.

The most common manifestations at disease onset were fatigue (22 [73%] of 30 individuals), arthralgia (21 [70%]), dryness (17 [57%]), parotid and submandibular gland swelling (15 [50%]), and skin rashes (ten [30%]). All children and young people diagnosed more than 3 years after disease onset (nine [100%] of nine) reported dryness compared with those diagnosed within 3 years (eight [38%] of 21; p=0·0014).

In terms of prevalence of rarer manifestations over the disease course, three (10%) of 30 individuals were diagnosed with renal involvement (one based on renal biopsy as tubulointerstitial nephritis and two on glomerulonephritis); three (10%) with manifestations of skin vasculitis (all based on skin biopsy); two (7%) with CNS involvement (one based on recurrent optic neuritis and transverse myelitis and one on seizures); and two (7%) with interstitial lung disease or bronchiectasis (table 2).

At last assessment, the median ESSDAI score was 2·0 (IQR 2·0–8·0), the median ESSPRI score was 5·3 (IQR 3·0–7·0), and 17 (57%) of 30 individuals with

| | Person 1 | Person 3 | Person 4 | Person 5 |
|---|---|---|---|---|
| Demographics | Age range 5–10 years, female, and Black African Caribbean | Age range 20–25 years, female, and White | Age range 25–28 years, female, and White | Age range 35–40 years, female, and Black |
| Type of lymphoma | MALT lymphoma diagnosed on parotid gland biopsy; localised lymphoma at diagnosis | MALT lymphoma diagnosed on parotid gland biopsy; advanced stage based on PET–CT assessment at diagnosis | MALT lymphoma diagnosed on parotid gland biopsy; PET–CT staging showed no widespread lymphadenopathy | Peripheral T-cell non-Hodgkin lymphoma with lymphadenopathy or skin involvement diagnosed on lymph node and skin biopsy; advanced stage based on PET–CT assessment at diagnosis |
| Disease characteristics | | | | |
| Diagnosis | Childhood-onset Sjögren's disease | Childhood-onset Sjögren's disease | Childhood-onset Sjögren's disease | Childhood-onset Sjögren's disease associated with childhood-onset SLE |
| Age range at diagnosis | 5–10 years | 15–20 years | 10–15 years | 5–10 years |
| Age range and disease duration at lymphoma diagnosis | 5–10 years; 0 | 15–20 years; 3 years | 25–30 years; 16 years | 15–20 years; 12 years for both conditions |
| Disease duration at last assessment | 8 years, lost to follow-up as not symptomatic | 6 years | 16 years | 29 years |
| Cumulative clinical features before lymphoma diagnosis | Only glandular manifestations (parotid enlargement), no dryness | Mild dryness, parotitis | Constitutional symptoms (eg, lymphadenopathy, parotitis, and dryness), haematological manifestations, arthralgia, and fatigue | Dryness but no obvious glandular enlargement; constitutional symptoms, arthralgia, fatigue in the context of childhood-onset Sjögren's disease; class III lupus nephritis, CNS lupus, panniculitis, cutaneous vasculitis in the context of childhood-onset SLE |
| Cumulative serological features before lymphoma diagnosis | Antinuclear antibodies and anti-Ro positive; borderline increased IgG | Positive for antinuclear antibodies, anti-Ro, anti-La, ribonucleoprotein, and rheumatoid factor positive; borderline increased IgG; cell counts within normal limit | Low white cell count; increased LDH; positive for antinuclear antibodies, anti-Ro, and anti-La; rheumatoid factor negative; normal IgG throughout disease course and only borderline increased at the time of diagnosis; normal C3 and C4 concentrations | Positive for antinuclear antibodies, anti-Ro, anti-La, and ribonucleoprotein; double stranded DNA positive; hypogammaglobulinaemia post-treatment with rituximab and cyclophosphamide, but normal IgG throughout disease course |
| Positive salivary gland biopsy before lymphoma diagnosis | Not done as lymphoma diagnosed at disease onset | Not done as serology and ultrasound suggestive of childhood-onset Sjögren's disease | Positive biopsy (focus score ≥1) | Positive biopsy (focus score ≥1) |
| Criteria fulfilled (including biopsy) at lymphoma diagnosis | | | | |
| 2016 ACR–EULAR classification criteria | Fulfilled | Fulfilled | Fulfilled | Fulfilled |
| Paediatric diagnostic criteria[2] | Not fulfilled | Fulfilled | Fulfilled | Fulfilled |
| Definite or probable childhood-onset Sjögren's disease diagnosis[4] | Yes | Yes | Yes | Yes |
| Probable or childhood-onset Sjögren's disease diagnosis[9] | Yes | Yes | Yes | Yes |

(Table 3 continues on next page)

| | Person 1 | Person 3 | Person 4 | Person 5 |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Disease trajectory assessments, lymphoma treatment, and outcome at last assessment | | | | |
| Median and mean ESSDAI | 0; 2·6 | 1·0; 3·0 | 4·0; 3·7 | 0; 2·3 |
| Median and mean ESSPRI | Data not collected in paediatric service | 2·0; 3·5 | 6·0; 6·4 | 6·4; 6·7 |
| SSDDI* | 5 | 5 | 7 | 7 |
| Cumulative treatment before lymphoma diagnosis | No treatment | Artificial saliva | Hydroxychloroquine, azathioprine, methotrexate, and four courses of rituximab; pilocarpine; and saliva and tear substitution | Mycophenolate mofetil, hydroxychloroquine, rituximab, and intravenous methylprednisolone (mainly for childhood-onset SLE manifestations); pilocarpine; and saliva and tear substitution |
| Lymphoma, treatment, and outcome | Successfully treated with surgery in paediatric service; no recurrence at last assessment; not on any treatment at last assessment as no dryness | MALT lymphoma treated successfully with radiotherapy; resolution on PET–CT assessment at last follow-up; saliva and tear substitution; refused hydroxychloroquine and pilocarpine as sicca symptoms manageable | Undergoing staging and due to start treatment for lymphoma; hydroxychloroquine; and saliva and tear substitution | Refused CHOP regimen, treated with rituximab (seven courses in total), cyclophosphamide (two courses), and intravenous methylprednisolone for concomitant childhood-onset SLE manifestations at time of lymphoma diagnosis (lupus nephritis, neuropsychiatric lupus, cutaneous vasculitis), leading to lymphoma remission; resolution on PET–CT assessment at last follow-up and skin manifestations resolved; hydroxychloroquine, mycophenolate mofetil, and IgG supplementation |
| Mapping onto NSST-derived adult clinical phenotypes | Data not available at diagnosis in paediatric service, but very likely low symptoms burden | Low symptom burden | High symptom burden | High symptom burden |

CHOP=cyclophosphamide, doxorubicin hydrochloride, vincristine sulphate, and prednisone. ESSDAI=EULAR Sjögren's syndrome disease activity index. ESSPRI=EULAR Sjögren's syndrome patient-reported index. MALT=mucosa-associated lymphoid tissue. NSST=Newcastle Sjögren's Stratification Tool. SLE=systemic lupus erythematosus. SSDDI=Sjögren's syndrome damage disease index. *5 points given for lymphoma.

***Table* 3: Characterisation of individuals with childhood-onset Sjögren's disease with lymphoma complications**

childhood-onset Sjögren's disease already had damage associated with an objective decrease in saliva or tear secretion (SSDDI score ≥1). Of 17 individuals who accumulated damage at the last assessment, three (18%) already had tooth loss (SSDDI score 3) and four (29%) had an SSDDI score of 5 or more because of a concomitant lymphoma diagnosis. Data were available for the whole cohort.

Cumulatively, all individuals with childhood-onset Sjögren's disease had clinically significant fatigue, 27 (90%) had clinically significant dryness, and 28 (93%) had clinically significant arthralgia. These symptoms were considered clinically significant if rated ≥5 of 10 on a visual analogue scale for each of the ESSPRI domains (as per the threshold for significant symptoms) at more than 50% of routine appointments that recorded ESSPRI data. ESSPRI data were available for only 22 individuals.

All but one individual with childhood-onset Sjögren's disease was positive for antinuclear antibodies, whereas 25 (83%) of 30 were positive for anti-Ro antibodies, 12 (40%) for anti-La antibodies, and 13 (43%) for rheumatoid factor. Eight (27%) of 30 individuals had high serum IgG concentrations (>20 g/L, as per the ESSDAI biological domain threshold), whereas ten (33%) had abnormally increased IgG concentrations (lab upper limit was 12 g/L or 16 g/L, depending on age) at the first assessment in paediatric or adolescent rheumatology clinics. Seven (23%) of 30 individuals treated with rituximab throughout the disease course for symptoms of skin vasculitis, renal or neurological involvement, refractory glandular swelling, or lymphoma had a decrease in IgG concentration post-treatment, with two developing iatrogenic hypogammaglobulinemia after four and seven rituximab courses, respectively. In Person 5 with childhood-onset SLE and associated childhood-onset Sjögren's disease with positive salivary gland biopsy, rituximab treatment was associated with two additional cyclophosphamide courses given at two different timepoints for severe lupus nephritis and CNS lupus (table 3). Treatment with mycophenolate mofetil, associated or not with rituximab, also led to a decrease in IgG concentration over the disease course in three (38%) of eight individuals. However, none had hypogammaglobulinemia. Data on lymphoma diagnosis were available for the whole cohort.

Only 20 individuals were evaluated for amylase serum concentration at diagnosis, seven of whom had increased concentrations. Cumulatively at the last assessment, 12 (40%) of 30 had at least two serum amylase concentrations above the upper limit of normal. There were no changes in the autoantibody profile over time in relation to seropositivity for antinuclear antibodies, anti-Ro, anti-La, and rheumatoid factor (data were available for the whole cohort).

All individuals had features suggestive of childhood-onset Sjögren's disease on imaging assessment of the exocrine glands, which eventually facilitated diagnosis based on expert opinion (100%). This might explain why

a small proportion (12 [40%] of 30 individuals) had a positive minor salivary gland biopsy and a larger proportion (21 [70%] of 30) fulfilled the clinical tool for childhood-onset Sjögren's disease diagnosis by Stern and colleagues,[9] which emphasises the role of glandular imaging in supporting childhood-onset Sjögren's disease diagnosis.

Ultrasound of the salivary glands (parotid and submandibular) supported the diagnosis of childhood-onset Sjögren's disease in 27 (90%) of 30 individuals based on the presence of mild, diffuse inhomogeneity with small hypoechoic foci (OMERACT score 1), moderate or severe diffuse inhomogeneity with multiple small hypoechoic areas (OMERACT score 2), or extensive inhomogeneity with hypoechoic or anechoic areas occupying the entire glandular surface or severe glandular atrophy (OMERACT score 3).[16] At diagnosis, 20 (74%) of 27 individuals had an OMERACT score of 1, four (15%) had a score of 2 , and three (11%) had a score of 3.

Sialography, in addition to ultrasound, was performed in three (10%) of 30 individuals mainly for therapeutic purposes (eg, methylpredisolone washouts to address persistent glandular swelling), and was suggestive of childhood-onset Sjögren's disease diagnosis based on a Rubin–Holt stage of ≥1.[19]

Three individuals had lachrymal involvement-associated lachrymal glandular enlargement on MRI and features of dacryoadenitis with lymphocytic infiltrate (focus score ≥1) on lachrymal gland biopsy, which excluded granulomas or histological features of IgG4-related disease, thus supporting the diagnosis of childhood-onset Sjögren's disease. All three individuals had ocular and oral dryness, but there were no findings suggestive of Sjögren's disease on the ultrasound examination of salivary glands.

Four individuals with childhood-onset Sjögren's disease were diagnosed with lymphoma over the disease course, three of whom were diagnosed with mucosa-associated lymphoid tissue lymphoma; one aged 5–10 years at childhood-onset Sjögren's disease diagnosis and two aged 15–20 years and 25–30 years (approximately 3 years and 16 years after childhood-onset Sjögren's disease diagnosis, respectively). Another individual with a previous diagnosis of childhood-onset Sjögren's disease associated with childhood-onset SLE was diagnosed with peripheral T-cell non-Hodgkin lymphoma with lymph nodes and skin involvement at age 15–20 years (12 years after onset of childhood-onset SLE and childhood-onset Sjögren's disease). Data on lymphoma outcomes were available in all four individuals. Three individuals with childhood-onset Sjögren's disease and concomitant lymphoma had fully recovered following radiotherapy (n=1) or chemotherapy (n=2) at the last assessment and one individual is undergoing chemotherapy.

Despite the absence of approved therapies for use in childhood-onset Sjögren's disease, several conventional and biological disease-modifying antirheumatic drugs (DMARDs) were used for glandular and extra-glandular manifestations. Each individual with objective evidence of decreased saliva secretion (as per oral medicine specialist assessment) was recommended high fluoride toothpaste. Saliva and tear stimulation strategies and supplementation were recommended to all individuals with symptomatic dryness. Pilocarpine (M1–3 muscarinic receptor agonist) was prescribed in nine (30%) of 30 individuals because of severe dryness-associated symptoms. Five individuals subsequently discontinued the treatment because of side-effects.

At diagnosis, 15 (50%) of 30 individuals were started on at least one conventional synthetic DMARD, most frequently hydroxychloroquine, as per clinician opinion (table 2). 15 (50%) of 30 individuals did not have specific manifestations or serological activity to grant systemic therapy. One individual initially refused treatment despite evidence of systemic manifestations (ie, vasculitis and arthritis managed with prednisolone alone) and accepted a subsequent trial of hydroxychloroquine in combination with azathioprine followed by methotrexate. However, all treatments were discontinued because of side effects. Conversely, two individuals with severe dryness and diagnostic biopsy of childhood-onset Sjögren's disease, but without systemic manifestations or serological activity, wanted to try several conventional synthetic DMARDs despite understanding that the evidence for their efficacy is poor and they are not routinely recommended. We subsequently offered 6-month therapeutic trials of conventional synthetic DMARDs, which were later discontinued as there was no evidence of effect on symptoms.

Cumulatively, as assessed at the last follow-up, eight (27%) of 30 individuals were treated with short courses of prednisolone: 25 (83%) with hydroxychloroquine, 11 (37%) with azathioprine, eight (27%) with mycophenolate mofetil, and seven (23%) with methotrexate. Treatment with belimumab (for a concomitant diagnosis of childhood-onset SLE with musculoskeletal and mucocutaneous manifestations) or adalimumab or baricitinib (for a concomitant diagnosis of juvenile idiopathic arthritis) was used in one individual each (3%), whereas three (10%) were treated with cyclophosphamide alone or in combination with rituximab for more severe or refractory manifestations (eg, skin vasculitis and pulmonary and neurological manifestations). Seven individuals were treated with rituximab (followed by mycophenolate mofetil or azathioprine) throughout the disease course for severe manifestations of transverse myelitis and optic neuritis (n=1, severe case with five recurrent episodes of optic neuritis), biopsy-proven tubulointerstitial nephritis (n=1), glomerulonephritis (n=2), refractory glandular manifestations (n=2), and skin vasculitis (n=1), as per current treatment recommendations[6,20] and paediatric and adult studies.[8,21–23] In this cohort, over the duration of follow-up,

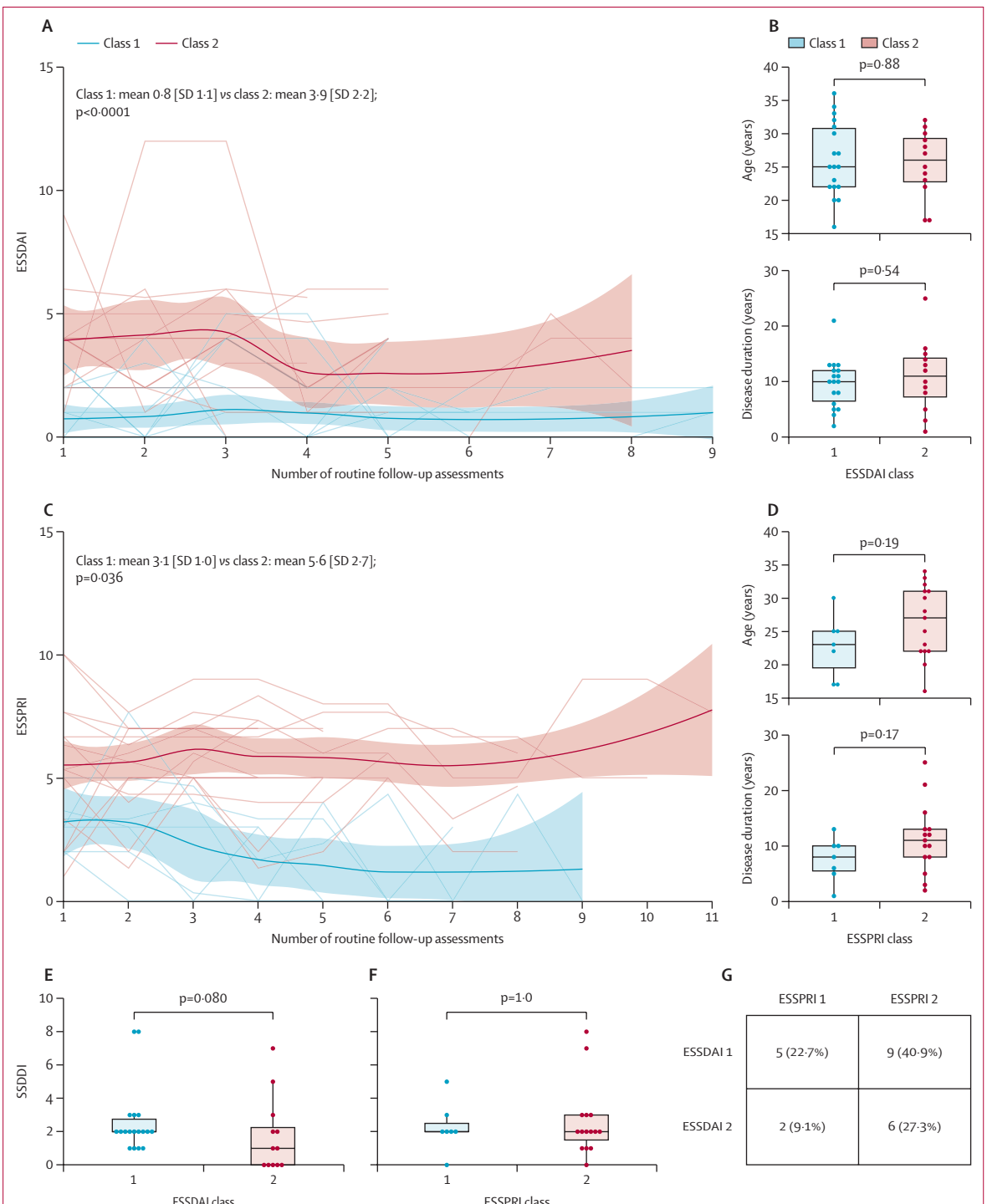


***Figure:*** **Evaluation of childhood-onset Sjögren's disease trajectories over time and the potential predictors**
(A) Trajectory of ESSDAI scores over time in two latent classes (class 1 and class 2) identified by trajectory analysis using latent class growth analysis. Each line represents an individual's ESSDAI score. Shaded areas indicate the 95% CI of the class-specific trajectories. (B) Comparison of age and disease duration between the two ESSDAI classes. (C) Trajectory of ESSPRI scores over time in class 1 and class 2. Each line represents an individual's ESSPRI score. Shaded areas indicate the 95% CI of the class-specific trajectories. (D) Comparison of age and disease duration between the two ESSPRI classes. (E) Comparison of SSDDI scores (ie, damage) between the two ESSDAI classes. (F) Comparison of SSDDI scores (ie, damage) between the two ESSPRI classes. (G) Overlap of the high versus low activity (ESSDAI) and symptoms (ESSPRI) trajectories over the disease course. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. SSDDI=Sjögren's Syndrome Disease Damage Index.

only five (17%) of 30 individuals had not been treated with any DMARDs, with the largest proportion (25 [83%]) having at least been prescribed hydroxychloroquine.

We identified two distinct ESSDAI trajectories over the disease course: high ESSDAI (mean 3·9 [SD 2·2], n=12) versus low ESSDAI (mean 0·8 [1·1], n=18; p<0·0001; figure A, B). These trajectories were not characterised by differences in sex, age, disease duration, length of follow-up, autoantibodies or medications. This finding suggests a possible underlying distinct molecular mechanisms driving the two phenotypes. As expected, the group with higher ESSDAI had a larger proportion of individuals with serum IgG concentration higher than 20 g/L (nine [75%] of 12) than the group with lower ESSDAI (four [22%] of 18; p=0·0021). Each distinct ESSDAI trajectory group included two individuals with lymphoma, suggesting that the trajectory analysis could not predict the risk of lymphoma.

Additionally, within the data availability, we also evaluated the ESSPRI trajectories during adolescence and young adulthood (ie, ages 13–36 years). Data collected at more than four different timepoints, including the most recent assessment, were available for 22 (73%) of 30 individuals with childhood-onset Sjögren's disease. We identified two distinct ESSPRI trajectories: high ESSPRI (mean 5·6 [SD 2·7], n=15) versus low ESSPRI (mean 3·1 [1·0], n=7; p=0·036), which were not associated with any statistically significant differences in disease features (appendix p 2) probably due to the small sample size (figure C, D). However, there was a trend towards longer disease duration and older age in individuals with high ESSPRI, which might reflect the effect of disease chronicity on patient-reported outcomes (figure D). This finding requires further validation.

See Online for appendix

Although there was no statistically significant difference between the SSDDI scores at the last assessment between the high disease ESSDAI trajectory (median 1 [IQR 0–2·5]) and low disease ESSDAI trajectory (2 [1–3]; p=0·080), the less active group accumulated more damage (ie, higher SSDDI score; figure E). This association is probably explained by the high prevalence of glandular damage and the limitation of the ESSDAI score in capturing glandular activity outside glandular swelling. The median SSDDI scores between the high symptom (2 [1–3]) and low symptom ESSPRI trajectories were similar (2 [2–3]; p=1·0; figure F).

For the sub-cohort (n=22) with complete data on ESSDAI and ESSPRI, only six (27%) of 22 individuals had a high disease activity trajectory based on ESSDAI assessment over time and high disease symptoms based on ESSPRI. Five (23%) of 22 individuals had low disease activity and low symptom trajectory, two of whom had higher disease activity and low symptoms over time and nine of whom had low disease activity and high ESSPRI scores over the disease course (figure G). This finding highlights the disconnect between the objective evaluation of childhood-onset Sjögren's disease activity and subjective assessment of symptoms. It is not dissimilar to the trend observed in adults with Sjögren's disease, most of whom reported high symptom burden in the context of low disease activity.[24]

## Discussion

This analysis of the largest childhood-onset Sjögren's disease cohort in the UK with long-term follow-up highlights an important unmet need for improved tools to facilitate early diagnosis and phenotype characterisation of childhood-onset Sjögren's disease to enable adequate management. This cohort had a female predominance that aligns with other cohorts and case-reports published in the literature.[5,8]

Although this cohort has been diagnosed historically based on expert opinion supported by suggestive investigations, when we evaluated the diagnostic workup used against the algorithm for diagnosing childhood-onset Sjögren's disease in children,[9] most cases followed a distinct step-up approach. This algorithm also advocates for performing minor salivary gland biopsy only, when necessary, especially in those with anti-Ro antibody positivity, and for a wider use of non-invasive salivary gland ultrasounds, which also reflects our practice.

Because salivary gland ultrasound is not included in any of the current diagnostic and classification criteria for childhood-onset Sjögren's disease or adult Sjögren's disease, a considerable proportion of individuals in this cohort did not fulfil these criteria.

The British Society of Rheumatology recently proposed[25] and published[6] the first guideline for management of Sjögren's disease across the life course, which does not recommend routine use of conventional synthetic and biological DMARDs, except for specific organ involvement or refractory manifestations, which reflects our therapeutic strategies.

This study generated key findings that contribute to an improved understanding of long-term outcomes of childhood-onset Sjögren's disease. Overall, individuals with childhood-onset Sjögren's disease overall had reasonably well-controlled disease at the last assessment based on ESSDAI assessment (median score of 2) that suggested low disease activity.[12] This finding shows that despite the absence of high-quality evidence of efficacy of DMARDs in adult Sjögren's disease, many DMARDs were beneficial in controlling organ-specific manifestations of childhood-onset Sjögren's disease or serological activity. Although no validated patient-reported outcome measures exist for use in childhood-onset Sjögren's disease, ESSPRI was a useful tool for capturing the impact of three cardinal domains of Sjögren's disease symptoms. At the last assessment, the median ESSPRI score of 5·3 (IQR 3·0–7·0) reflects the recognised dichotomy between the objective and subjective assessment of disease severity widely reported in adult Sjögren's disease.[26] Although none of these

outcome measures are validated for use in paediatric populations, it is highly likely that the ESSDAI assessment performs similarly as in adults with childhood-onset Sjögren's disease as the glandular and constitutional domains that are the most frequently affected in children are captured by this score. Regarding the ESSPRI assessment, it is possible that the lower prevalence of dryness and the higher frequency of glandular enlargement that is not evaluated by this score might lead to a less reliable estimation of symptom impact in childhood-onset Sjögren's disease. Even with these caveats, there was evidence of moderate ESSPRI scores overall at the last assessment, reflecting similar management challenges as encountered in adults with Sjögren's disease.[27]

A large proportion of this cohort has acquired damage within the glandular domain (17 [57%] of 30), predominantly due to objective decrease in saliva or tears, with three (18%) of 17 already having tooth loss in early adulthood, which might suggest a lost window of opportunity to halt the autoimmune glandular insult with the current therapeutic approaches. Individuals who developed lymphoma (four [13%] of 30 in this cohort) had the highest damage scores, although three (75%) of four had good outcomes following treatment, while one is currently undergoing therapy.

The therapeutic strategies used in this cohort reflect the restrictions in accessing B-cell depletion therapy. Despite these treatments being recommended for refractory glandular involvement by the 2020 EULAR recommendations for management of adult Sjögren's disease,[20] they are not available to prescribe for children and young people in England and many other countries worldwide. We used rituximab in only two of eight individuals with refractory glandular swelling but could not secure approval for the use of belimumab or JAK inhibitors. Therefore, we had to rely on repeated courses of oral or glandular prednisolone washouts.

The combination of rituximab with mycophenolate mofetil or cyclophosphamide led to good outcomes in individuals with skin vasculitis and renal and CNS manifestations, as well as resolution of clinical, functional, and imaging abnormalities encountered in one individual diagnosed with mild interstitial lung disease, suggesting that early recognition and prompt immunosuppressive treatment are associated with good outcomes in childhood-onset Sjögren's disease. Similarly, treatment with prednisolone, methotrexate, and azathioprine led to complete resolution of myositis in two individuals. The individual with bronchiectasis (complication described as associated with older age and lower frequency of autoantibodies in adult Sjögren's disease,[28] was positive for anti-Ro and anti-La, did not respond to DMARD therapy, and continued to have severe respiratory infections.

We acknowledge the differences in the demographics, sex ratio, and classification of this cohort compared with cohorts in other reports, including cohorts evaluated by general paediatricians[29] or oral medicine specialists or dentists.[3] This disparity reflects the potential stringency our hospital applied to accepting referrals and why, at first review in our rheumatology services, many children and young people already had positive investigations, which reduced the suitability of applying the Florida Scoring System diagnostic tool to this cohort.

The main limitations of this study are related to the small sample size, partial retrospective data collection, and single-centre study design. Additionally, we were only able to perform a sub-analysis of the ESSPRI trajectories over time as data were available for only 22 (73%) of 30 individuals. Within the caveat of the small sample size, we stratified children and young people with childhood-onset Sjögren's disease in two distinct groups based on disease activity and symptom severity and identified concordance in 15 (50%) of 30 individuals. This finding highlights the disease heterogeneity and potential need for tailored management approaches to address disease control and impact of symptoms. Future research in larger cohorts should explore the use of ESSDAI and ESSPRI as multiple latent class variables to see whether they drive different cohort stratification. Despite the small sample size, this study provides a unique understanding of long-term outcomes of childhood-onset Sjögren's disease into adulthood and supports our recommendation for research into identifying the molecular drivers of distinct childhood-onset Sjögren's disease endotypes, similar to what has been achieved in adults.[30] Such research could help to identify early tailored interventions in childhood-onset Sjögren's disease, which might prevent high symptom trajectory over the life course. Further validation in larger cohorts with long-term follow-up is also required to evaluate the damage and malignancy risk in childhood-onset Sjögren's disease during the life course and address the high symptom burden, which calls for collaborative and multinational efforts to support high-quality research.

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**Contributors**
CC conceptualised the project, and contributed to data collection, data curation, formal analysis, methodology, supervision, and original draft writing, review, and editing. JP performed analyses and contributed to the draft writing, review, and editing. RG, RW, HP, and MAO contributed to data collection and curation, and project administration. ECJ contributed to the original draft writing, review, and editing. All authors reviewed and approved the final version of the manuscript. All

authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. CC and JP directly accessed and verified the underlying data reported in the manuscript.

#### Declaration of interests

CC reports a research grant from GSK and speaker honoraria from Novartis. RW reports speaker honoraria from Novartis, and support for attending the 2025 British Society for Rheumatology annual meeting from Medac. All other authors declare no competing interests.

#### Data sharing

Data collected for the study (de-identified participant data), including related documents (eg, study protocol, statistical analysis plan, and informed consent form) will be available on request from the date of publication.

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