ASSESSING THE RISK OF SYSTEMIC DISEASE IN CHILDREN WHO PRESENT TO PRIMARY CARE WITH MOUTH ULCERS.

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master in Philosophy by

Natasha Jade Carter Goss

July 2022

Institute of Life Course and Medical Sciences (ILCMS)

Supervisors:

Professor M. W. Beresford

Dr C. Pain

Dr C. Fleming

Declaration

This thesis is the result of my own work. The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part for any other degree or qualification.

The research was carried out within the Department of Women's and Children's Health, Institute of Life Course and Medical Sciences.

Natasha Goss

Abstract

Background

Mouth ulcers are a common complaint, particularly amongst children and young people (CYP). Usually, they are benign and self-limiting with minimal or no intervention. However, it is known they can sometimes be the presenting symptom of more serious systemic diseases. Three systemic disease exemplars are selected in this thesis, namely: systemic lupus erythematous (SLE), Behcet's disease and inflammatory bowel disease (IBD). These complex disorders all can include oral ulceration. It is unknown the risk of subsequent systemic disease in a CYP who presents with mouth ulcers. This thesis will investigate the current knowledge, patient and public opinion and primary care data on this topic.

Aims

1. To determine the current evidence base for outcomes of CYP with mouth ulcers, through a systematic review of the existing literature, specifically their risk of developing a systemic disease following presentation of mouth ulcers to a healthcare setting.
2. To understand the impact of this study on patients and their families through a programme of patient and public involvement research, to ensure study findings inform the subsequent Clinical Practice Research Datalink (CPRD) study, including how results and outcomes are presented.
3. To determine the risk of developing a serious systemic inflammatory condition in CYP who present to primary care with mouth ulcers by collecting data from the CPRD.

Methods

Three study designs combined to assess mouth ulcers in systemic disease, each sequentially informing the next. A systematic review assessed current literature relating to progression from mouth ulcers to systemic disease diagnosis. Patient and public involvement and engagement (PPIE) collated opinion on each aspect of the study. Informed by these studies, a cohort study investigated anonymised, electronic, primary care records from the Clinical Practice Research Datalink (CPRD) between 1990 and 2019. The association between the presentation of mouth ulcers the subsequent diagnosis of systemic disease was assessed quantitively through incidence rate and rate ratios.

Results

- 142 manuscripts were included in the systematic review. None assessed risk of developing systemic disease, specifically SLE, Behcet's or IBD, in children who present to a healthcare setting. The review highlighted that further research was required to assess associated non-mouth ulcer presenting symptoms and from time lag presentation to diagnosis, as well as the contribution of age, sex and ethnicity. Primary care was an area that particularly lacked literature on this topic.
- 272 participants contributed to PPIE input. Responses in all groups provided some support for the proposed cohort study outcomes. However, they also highlighted that care must be taken when applying results to clinical practice especially when communicating risk.
- 520,034 CYP were analysed in the CPRD cohort study, including those with and without a code for mouth ulcers. The incidence rate of any of the three systemic diseases was considerably higher in the CYP with mouth ulcers coded for in their record, compared to those without: the incidence rate ratio was 76.2 (46.2-125.9) when exposed and unexposed populations were compared.

Conclusion

This thesis identified gaps in the current literature relating to the risk of systemic disease in CYP with mouth ulcer. Alongside PPIE input, these informed a cohort study of CPRD data. The study concluded that children with a mouth ulcer code in primary care are at higher risk of a subsequent systemic disease diagnosis. Areas for further research were identified in all three stages of the study.

Acknowledgements

This work would have not been possible without the support, input and words of encouragement from numerous people.

Firstly, I must thank my family, partner and friends for their unwavering support throughout my studies.

Secondly, I would like to thank Dr Pieta Schofield from the Department of Public Health, Policy and Systems at University of Liverpool, for the countless hours she has contributed in extracting CPRD data and providing analytical support. Without this, the CPRD study would not have been possible, nor would the results have been accurate. Behcet's UK must be acknowledged for providing funding for the IMD data used in the analysis, which provided important insight into the effect of socioeconomic deprivation in this study.

Next, I would like to thank Simon Perkins, Eva Caamano-Gutierrez and the rest of the Computational Biology Facility (CBF) team who provided a very informative R course which formed the basis of my cohort data analysis. The 1:1 support provided after the course was instrumental in allowing the data analysis to commence. I would also like to acknowledge that my attendance of this course was funded by a delegate bursary provided by the University of Liverpool.

For assistance with the systematic review portion of this thesis in the form of reviewing a great deal of manuscripts for inclusion/exclusion, I would like to Katie Murray and Lily Jones. I appreciate the time they took out of their own to improve the validity of the systematic review results.

There are many people and organisations to thank for their contribution to the Patient and Public Involvement and Engagement (PPIE) section of this this. Behcet's UK, Lupus UK and Crohn's and colitis UK must be acknowledged for disseminating surveys; Sammy Ainsworth with GenR Liverpool and Laura Lunt with YourRheum for facilitating PPIE meetings and patiently educating about PPIE research; and particularly all of the young people, patients and parents who gave up their time to contribute to PPIE input. The contribution of their views allowed this research to be acceptable and relevant to the people it aims to benefit.

Finally, I would like to acknowledge the support of my supervisors, Prof. Michael Beresford, Dr Clare Pain and Dr Kate Fleming, throughout this challenging year. The opportunity to undertake this MPhil under their supervision, and their guidance throughout has been invaluable to not only this thesis, but to my academic and personal development this year.

Contents

List of Tables

List of Figures

List of abbreviations

ACR= American College of Rheumatology

CBF= Computational Biology Facility

CD= Crohn's disease

CEBM= Centre of Evidence Based Medicine

CPRD= Clinical Practice Research Datalink

CYP= children and young people

EATC4C= Experimental Arthritis Treatment Centre for Children

EIMs= extraintestinal manifestations

FMF= familial Mediterranean fever

GP= general practitioner

IBD= inflammatory bowel disease

ICBD= International Criteria for Behcet's Disease

ICO= Information Commissioner's Office

IMD= Index of Multiple Deprivation

IRR= Incidence rate ratio

ISG= International Study Group

PFAPA= periodic fever, aphthous stomatitis, pharyngitis and adenopathy

PPIE= Patient and Public Involvement and Engagement

QOF= Quality and Outcomes Framework

RAS= recurrent aphthous stomatitis

RDG= Research Data Governance

SHARE= Single Hub and Access point for paediatric Rheumatology in Europe

SLE= systemic lupus erythematous

SLICC= Systemic Lupus International Collaborating Clinics

TRAPS= TNF-α Receptor-Associated Periodic Syndrome

UC= ulcerative colitis

UoL= The University of Liverpool

YPAG= Young Persons Advisory Group

1 Chapter 1: Introduction

1.1 Background

There are approximately 12.7 million children and young people (CYP) under the age of 16 years in the UK (1). With a prevalence of approximately 9% (2), mouth ulcers are a common complaint in childhood, affecting about 1.1 million UK CYP. Due to variance in health seeking behaviours this is likely an underestimation, especially in terms of transient ulceration. Most ulcers are usually benign and self-limiting, lasting less than 2 weeks. However, some become recurrent with repeated episodes differentiated by intermittent healing (3). Peak prevalence of recurrent ulcers is seen at ages 10-19 years although severity and frequency of multiple ulcers declines with age (4).

Ulcers within the oral cavity cause local pain and inflammation. This can result in the primary morbidity in the paediatric population which is dehydration due to reduced oral intake (4). Complications can also arise with a CYP's resistance to eating or tooth brushing during flares, leading to weight loss and dental decay respectively. Most cases are treated at home with supportive care and/or with over the counter treatments. It is not known what proportion of cases present to primary care, nor the factors that prompt families to contact their GP regarding mouth ulcers in a CYP. There is no directly associated mortality associated with simple, solitary ulcers unless they are a symptom of a more significant illness. Evidence suggests that mouth ulcers may not only act as a symptom of certain immune-mediated conditions but can be a presenting complaint months or years before diagnosis.

The specific immune-mediated conditions of interest in this study are Behcet's disease, systemic lupus erythematous (SLE) and inflammatory bowel disease (IBD). These three conditions were selected since they are known to present with the common symptom of mouth ulcers, yet they are individually rare diagnoses in CYP. Hence it would be clinically useful to assess the risk associated with mouth ulcers for each and all of these conditions. Behcet's disease is a heterogenous vasculitis which manifests as mouth and genital ulcers as well as widespread involvement of the skin, eyes, joints, central nervous and gastrointestinal systems (5). The presence of these diagnostic symptoms occurs much less in the paediatric population compared to adults, with an incidence of 1.2 per million person-years in CYP under the age of 16yrs (6). SLE is defined as a chronic systemic autoimmune condition characterised by the development of autoantibodies directed against nuclear self-antigen, that is not limited to one organ system (7). Some 15-20% of all patients develop SLE in childhood, with childhood onset being rare with an incidence of 40-50 per million person-years (8). IBD can be categorised into Crohn's disease (CD) and ulcerative colitis (UC), both of which are chronic, idiopathic inflammation of the gut differentiated by which part of the system they affect (9). The overall incidence of IBD in CYP is 105

per million person-years(10), with CD being twice as common as UC (11). Although individually some of these conditions are rare, when combined together under the umbrella term of 'systemic diseases' (i.e. the disease affects multiple organ systems) the extent of the issue becomes much greater.

All three key systemic diseases listed above mention oral ulcers in their classification and/or diagnostic criteria (12-14), excluding the categorisation of typical UC. In the absence of diagnostic criteria, for example in SLE, classification is important in both clinical and research contexts. If oral ulcers are present at the time of clinician assessment they can be used to confirm or contribute to a diagnosis/ probable diagnosis or classification. The overall incidence of these three conditions combined is approximately 150 per million person-years in CYP under 16 years (6, 8, 10), compared to the approximately 15,000 per million person-years incidence of mouth ulcers (2)(calculated retrospectively). Therefore, mouth ulcers are clearly not always indicative of a systemic disease and only some children will progress from simple or recurrent mouth ulcers to a serious diagnosis. It is not yet known why some children follow this progression and some do not.

A previous (or resolved) presentation of oral ulceration in childhood is not however a proven precursor for any of the listed systemic diseases. This is partly because of the natural history of all causes of mouth ulcers, many of which are benign and self-limiting, but also as there is a lack of evidence base with no prospective studies looking into the progression from mouth ulcer presentation in childhood to the subsequent diagnosis of a systemic disease. Therefore, current predictions rely on individual clinicians' experiences. A more robust evidence base would help inform and clarify the concern that oral ulceration increases a child or young person's risk of developing a systemic disease and subsequent diagnosis. It would also be able to determine the contribution of other demographic factors and the variance with each condition. This would directly inform clinicians in counselling patients, and hence CYP and their families would benefit directly.

1.2 Aims of Thesis

This thesis will seek to understand the risk of developing a serious systemic inflammatory condition in CYP who present with recurrent mouth ulcers.

- Aim 1: To determine the current evidence base for the outcomes of CYP with mouth ulcers, through a systematic review of the existing literature, specifically their risk of developing a systemic disease following a presentation of mouth ulcers to a healthcare setting.
- Aim 2: To understand the impact of this study on patients and their families through a programme of patient and public involvement (PPIE) research, to ensure study findings inform

the subsequent Clinical Practice Research Datalink (CPRD) study, including how results and outcomes are presented.

- Aim 3: To determine the risk of developing a serious systemic inflammatory condition in CYP who present with mouth ulcers in a primary healthcare setting by collecting data from the CPRD.

1.3 Study designs

Three study designs were combined to assess the issue of mouth ulcers in systemic disease thoroughly and in the broadest context.

The first study was a systematic review assessing the question: *'Are CYP who present to a healthcare setting with mouth ulcers at an increased risk of developing a systemic disease, specifically SLE, Behcet's or IBD?'*. Using a systematic approach all relevant manuscripts were identified (as defined by the inclusion/ exclusion criteria, see *Section 2.2.3*), these studies had relevant data extracted from them. These data were reviewed for validity, combined, and presented as a series of key themes emerging from the existing literature. Together, these also directly inform the Patient and Public Involvement and Engagement (PPIE) surveys (*see Chapter 3*) and the subsequent detailed CPRD cohort study (see *Chapter 4*) which assessed the issue of mouth ulcers in CYP in further detail. The systematic review was able to draw its specific conclusions on the research question and gaps in literature.

The subsequent CPRD cohort study designs (see below) were underpinned by input from patients and their families. This was collected systematically through various PPIE activities. These activities included interactive Zoom meetings as well as online questionnaires targeted at specific patient groups. The relevance of this project and quality of the results and outputs emerging from the study including their subsequent messaging, distribution and dissemination were significantly enhanced by the thoughts and opinions of the people the project was aiming to help in the long term.

The cohort study then investigated anonymised, electronic, primary care records from the CPRD between 1990 and 2019. This time period was selected because the accuracy of the dataset is acceptable from 1990 onwards and to avoid the effect on the data of the COVID-19 pandemic in the years following 2019. The CPRD data set is a resource providing access to anonymised UK primary care records and other linked databases for the purposes of clinical and public health research. The resource has been active for more than 30 years and holds data on >60 million patient records from approximately 2,000 contributing practices (15), which are representative of the general UK population. The aim of the CPRD cohort study was to assess the association between the presentation

of mouth ulcers in primary care specifically, and the subsequent diagnosis of systemic disease. The risk of progression to a systemic disease, for CYP presenting with oral ulcers to their GP, was stratified by variables identified in the systematic review. It is anticipated that the results of this study will contribute to the current understanding of the issue and hence allow clinicians more confidence in offering the right management strategies to patients and their families.

This cohort study extracted data on a sample of CYP aged under 16 years from the CPRD in England, this sample included CYP with a code for mouth ulcers and a similar population (in age and sex) of CYP without mouth ulcers. Incidence rate and rate ratios were calculated to determine the risk associated with mouth ulcers in relation to systemic disease. Multifactorial analyses were used to determine if these risks are associated with other factors such as sex, age and socioeconomic status. Linked Index of Multiple Deprivation (IMD) data were utilised to detect potential differences in outcomes between socioeconomic groups, hence informing clinical practice to reduce healthcare inequalities in the long term.

2 Chapter 2: Systematic review

Are CYP who present to a healthcare setting with mouth ulcers at an increased risk of developing a systemic disease, specifically SLE, Behcet's or IBD?

2.1 Introduction

It is recognised that mouth ulcers can be a precursor to systemic disease in some children months or even years in advance. However, they are not always indicative of a systemic disease. It is not yet known which children with mouth ulcers will progress to a systemic disease diagnosis. Nor is it fully proven in the literature that previous or resolved mouth ulcer episodes are a precursor to systemic disease.

This lack of evidence is reflected in there being no published systematic review exploring the progression from mouth ulcer presentation in childhood to the subsequent diagnosis of a systemic disease. If evidence could be collated to answer the unresolved questions around systemic disease risk in children with mouth ulcers, and assess other contributing factors such as demographics, then clinicians, patients and families would be better informed for future decision making.

This review will assess the current evidence relating to the risk of progression from presentation of mouth ulcers to diagnosis of a systemic disease in childhood. The existing published data on this topic will be collected and presented along with assessment of the literature's validity. Following a preliminary consideration of the currently available evidence it is evident that there are significant gaps in knowledge on this topic. Overall, this review will be used to inform conversations with patients and their families (see *Chapter 3*) and the subsequent cohort study of the CPRD (see *Chapter 4*), seeking to address this overarching research question. The systematic review, patient and family inputs and cohort study combined will provide some of the further insight that is required on this topic.

2.1.1 Aims of Systematic Review

The aims of this review included:

1. To systematically assess the current literature relating to the risk of progression to SLE, Behcet's and/or IBD in children who present to a healthcare setting with mouth ulcers.
2. To summarise qualitative and quantitative aspects of the current literature.
3. To describe gaps in current knowledge and define recommendations for further study.

4. To use these data to inform conversations with patients and their families, and the subsequent CPRD study, with regards to outcomes and currently available data and statistics regarding mouth ulcers in CYP.

2.2 Methodology

2.2.1 Justification

A basic initial search with limited search terms was conducted in four scientific databases (Scopus, Ovid, Web of Science Core Collection and PubMed). The search terms in the initial search were: children/childhood/paediatric and mouth ulcer/ oral ulcer/aphthous stomatitis and systemic disease/ lupus/ SLE/IBD/ Crohn's/ ulcerative colitis/ UC/ coeliac/ Behcet's (results were restricted to manuscripts in English within the databases). These searches yielded 217 total results which was deemed sufficient to justify a full systematic review with this question.

2.2.2 Searches

Search terms were mapped to three main topics: children, mouth ulcers and systemic disease. *Table 1* summarises the final search terms, divided into these topics, along with the heading of each topic, also inputted as a search term. The terms were entered into the following databases: Scopus, Ovid, Web of Science Core Collection, PubMed, Cochrane Trials Register and opengrey.eu, in order to maximise capture of the majority of available literature. Search terms were combined using the 'AND' MESH term. All searches were conducted on 4th October 2021.

Table 1- Search terms divided by main topics

Children	**Mouth ulcer**	**Systemic disease**	
Child	Oral ulcer	SLE	Regional ileitis
Childhood	Lip ulcer	Lupus	Terminal ileitis
Juvenile	Aphthous stomatitis	Systemic lupus erythematous	Ileocolitis
Paediatric	Stomatitis	Lupus erythematous disseminatus	Crohn's enteritis
Teenager	Ulcerative gingivitis	Libman-Sacks	PFAPA
Adolescent	Ulcerative stomatitis	Behcet's	Coeliac
Adolescence		Behcet's syndrome	Coeliac sprue
Youth		Old silk route	Coeliac enteropathy
Teen		Behcet	Gluten-sensitive enteropathy
Infant		IBD	Nontropical sprue
		Inflammatory bowel	Inflammation
		Ulcerative colitis	Inflammatory
		UC	Immune-related
		Idiopathic proctocolitis	Immune-mediated
		Colitis gravis	Autoimmune
		Crohn's	Systemic vasculitis
		Granulomatous colitis	Systemic
		Granulomatous enteritis	Vascular
		Regional enteritis	

2.2.3 Inclusion/ exclusion criteria

Inclusion and exclusion criteria (*Table 2*) were decided upon *a priori* to conducting the searches and were applied once results had been collected. No date restrictions were applied since, to our best knowledge, there have been no systematic reviews specifically relating to this question performed previously. Hence manuscripts could date from the start of each database to the date of the search. Additional criteria such as 'English language' and 'human subjects' were applied at this stage. Remaining articles were transferred to the Rayyan systematic review software for further review, which allows online review of manuscripts as well as reviewer collaboration (https://www.rayyan.ai/). Duplicates were removed before the screening process commenced.

Table 2- Criteria for inclusion/exclusion

Inclusion	**Exclusion**
- English language - Human subjects - Level 1-3b evidence (and case series with >20 cases) - Subjects have mouth ulcers (aphthous stomatitis) - Paediatric population (<18yrs) or mixed population with extractable paediatric data. - Outcomes regarding risk of systemic disease from mouth ulcer presentation or describe initial presenting symptoms of systemic disease diagnosis. - Original research (not conference abstracts).	- Herpetic or non-oral ulcers - Ulcers related to infection or malignancy - Non-systemic disease - Level of evidence 4-5 (*Table 3*) - Drug trials

2.2.4 Screening

Each manuscript was screened by an independent reviewer and the principal author (NG) in the Rayyan software, based on the aforementioned criteria. Two independent reviewers helped with this process, each screening half of the manuscripts each due to the large number of search results. The screening process was conducted blind and in stages, firstly by title, then abstract and finally full text review. Any conflicts were discussed and resolved between all three reviewers. Once the final list of included manuscripts was complete, the reference lists of these manuscripts were screened using the same criteria to assess for further relevant manuscripts. Previously excluded literature reviews from the original search were also screened in an attempt to find all relevant manuscripts. A breakdown of the number of manuscripts included/ excluded at each stage is displayed in Section 2.3.1 *(Figure 1*).

2.2.5 Data extraction

All included manuscripts were collated in EndNote, including their full references, to aid data collection. Data was then collected and organised in Microsoft Excel. Manuscripts related to each condition of interest were listed on different excel worksheets. There was also a worksheet for 'other' conditions which included fever syndromes, coeliac disease and recurrent aphthous stomatitis, among others.

Standard headings were used on each sheet for general data collection which included title, date of publication, authors, country, summary of content, definition of disease, point in disease symptoms

were recorded at, number of patients, inclusion age, sex, ethnicity, age at disease onset and diagnosis respectively. An example of this can be seen in *Appendix A.*

From this information, the 'level of evidence' (*Table 3*) for each manuscript (based on Oxford (UK) Centre of Evidence Based Medicine (CEBM) Levels of Evidence (16)) was noted as an initial assessment of data reliability.

Table 3- Description of CEBM level of evidence (formatted from https://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=oxford)

Level of evidence	**Description**
1a	Systematic review (with homogeneity) of inception cohort studies; or a clinical decision rule validated in different populations.
1b	Individual inception cohort study with > 80% follow-up; or a clinical decision rule validated on a single population.
1c	All or none case-series.
2a	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in randomized controlled trials.
2b	Retrospective cohort study or follow-up of untreated control patients in a randomized controlled trial; or derivation of a clinical decision rule or validated on split-sample only.
2c	"Outcomes" research.
4	Case-series (and poor-quality prognostic cohort studies).
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

The frequency of children with each symptom was extracted from the manuscripts. Symptoms were added as new headings as they appeared in each manuscript unless the symptom heading had already been extracted from a previous manuscript. If symptoms were reported at more than one time point in the disease course, then this was noted and all data was extracted. Some comparison manuscripts divided data by sex, ethnicity or age, this data was combined for the purposes of this review. However, if a manuscript reported a significant difference between study groups for any given symptom this was recorded in the notes section of the data extraction spreadsheet.

2.3 Results

2.3.1 Definition of included manuscripts

A total of 2,964 manuscripts were identified following the initial literature search, plus manuscripts extracted from the reference lists of included manuscripts, with duplicates removed. Of these, 2,271 were excluded at the title/abstract screening stage based on the inclusion/ exclusion criteria, leaving 693 manuscripts to undergo full text review. Manuscripts were excluded at this second stage if they did not meet the aforementioned inclusion/exclusion criteria (*Table 1*), with specific examples for exclusion given in *Figure 1*. A total of 152 manuscripts were deemed satisfactory to be included in the literature review. The flow of manuscripts through the screening process can be seen in *Figure 1.*

Of note, no outcomes in any included manuscripts related to the risk of progression from mouth ulcers to systemic disease. Most stated qualitatively and quantitively the presenting and/or cumulative symptoms experienced by children with the systemic diseases of interest. Hence the following results are presented as per themes we expect the proposed CPRD study to clarify fully, in order to identify gaps in the current literature. For example, presenting symptoms, time lag, age, sex, ethnicity and access to healthcare. *Tables 4* and *5* give an overview of included manuscripts, including the demographic and reported symptom categories of the study cohorts, divided into the three systemic diseases.

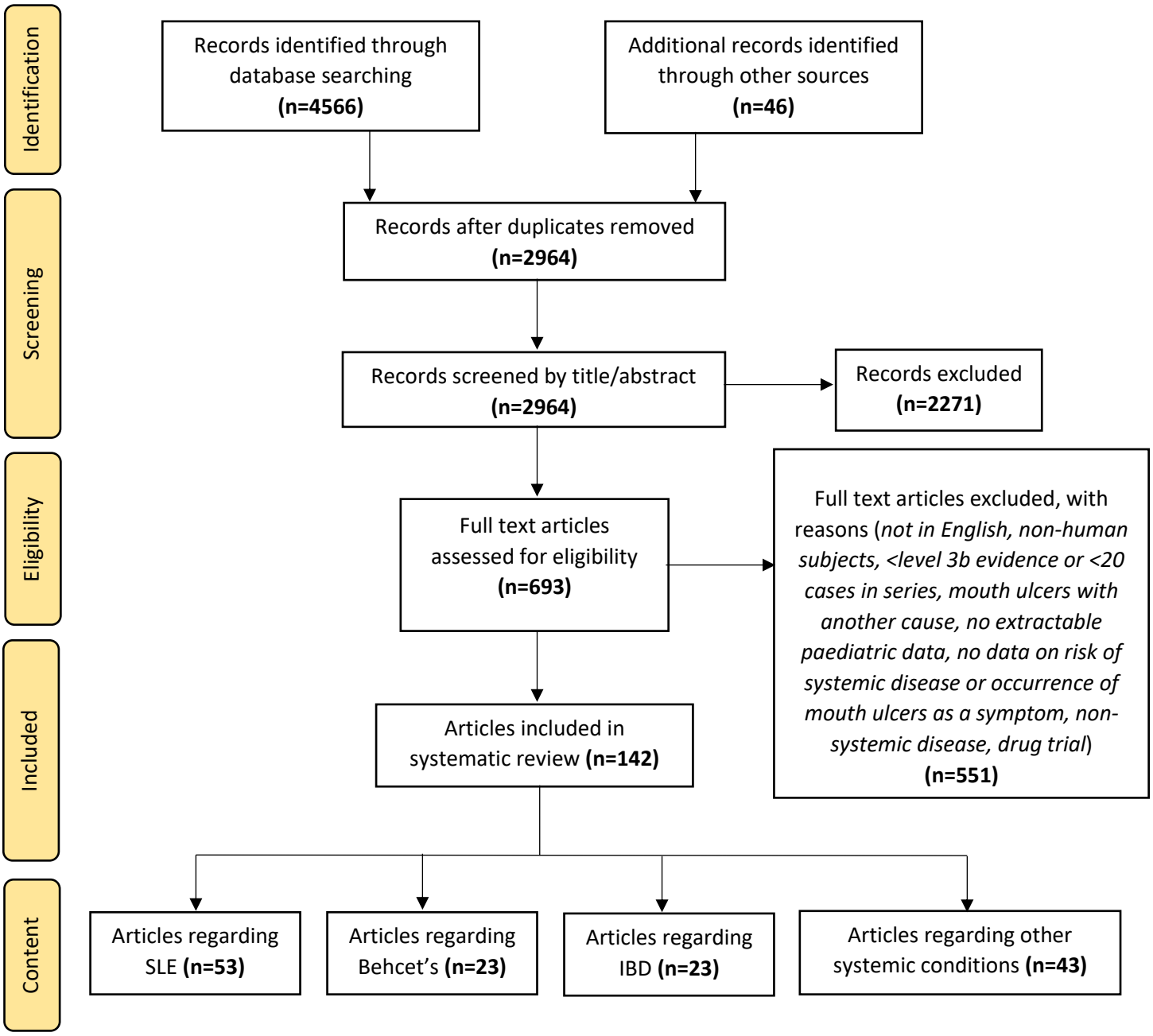

Figure 1- Flow diagram showing number of manuscripts at each stage of screening

Table 4- Overview of systematic review results: manuscript details and demographics

	SLE (n= 53*)	**Behcet's (n= 23^)**	**IBD (n= 23†)**
Manuscript details			
Date range	1977-2020	1993-2020	1971-2020
Number of manuscripts level 1b evidence (%)	9 (17)	3 (13)	8 (35)
Range of cohort size	20-847	23-2368	20-1649
Study design (number of manuscripts (%))			
Single centre descriptive, observational cohort/case series	3 (6)	-	1 (4)
Single centre cross-sectional	4 (8)	-	-
Multicentre cross-sectional	3 (6)	-	-
Single centre retrospective cohort	20 (38)	12 (52)	9 (39)
Multicentre retrospective cohort	14 (26)	8 (35)	5 (22)
Single centre prospective cohort	2 (4)		4 (17)
Multicentre prospective cohort	7 (13)	3 (13)	4 (17)
Demographics			
Range of female percentage *(% of manuscripts reported in)*	68-98 (98)	25-63(87)	12-66 (91)
Most commonly ethnic majority *(% of manuscripts ethnicity was reported in)*	Caucasian (64)	Turkish (48)	Caucasian (48)
Most common definition of disease *(% of manuscripts reporting disease definition in methodology)*	ACR criteria (96)	ISG criteria (91)	Clinical diagnosis (87)
Range of mean/median age at onset *(% of manuscripts reported in)*	7-15 (28)	5-13 (74)	9-14 (74)
Range of mean/ median age at diagnosis *(% of manuscripts reported in)*	8-18 (91)	9-15 (83)	-

**(17-69), ^(70-92), †(93-115)*

Table 5- Overview of systematic review results: symptom data

	SLE (53*)		**Behcet's (23^)**		**IBD (23†)**	
Symptom categories	No. of manuscripts referencing symptom category (%)	Frequency range at onset (%)	No. (%)	Freq. range (%)	No. (%)	Freq. range (%)
MSK	53 (100)	2-81	22 (96)	1-39	18 (78)	2-67
Renal (and pancreatic)	48 (91)	2-86	2 (8.7)	3	5 (22)	1-2
Skin lesions	52 (98)	1-91	23 (100)	1-82	16 (70)	1-2
Systemic/constitutional	37 (70)	4-91	5 (22)	21-77	18 (78)	4-79
Neurological	51 (96)	1-58	21 (91)	1-94	3 (13)	-
Mucocutaneous/ other ulcers/ other oral symptoms	37 (70)	1-89	22 (96)	2-69	2 (8.7)	-
Vascular	34 (64)	1-30	20 (87)	1-11	2 (8.7)	2
Abdominal/ gastrointestinal	12 (23)	1-14	19 (83)	1-52	12 (52)	9-88
Eye symptoms	8 (15)	3	23 (100)	2-27	7 (30)	2
Respiratory/ pulmonary	38 (72)	1-32	12 (52)	3	-	-
Cardiac	38 (72)	1-17	7 (30)	3	-	-
Hepatic	4 (7.5)	5-16	-	-	6 (26)	1-2
Others	33 (62)	2-28	1 (4.3)	7	-	-
Lymphatic	19 (36)	-	-	-	-	-
Haematological	47 (89)	2-94	-	-	-	-
Organomegaly	15 (28)	3-42	-	-	-	-
Genitourinary	-	-	8 (35)	1	-	-
Stools	-	-	-	-	12 (52)	10-93
Perianal	-	-	-	-	14 (61)	2-86
Intestinal complications	-	-	-	-	3 (13)	2-28

**(17-69), ^(70-92), †(93-115)*

2.3.2 Presenting symptoms

Mouth ulcers at onset were reported in 32 (60%) SLE manuscripts with a frequency range of 3-74% (17-33, 35, 36, 38-47, 49, 52, 53), and 3-21% (18-20, 27, 32) in the highest level of evidence manuscripts. Sixteen (70%) Behcet's manuscripts reported mouth ulcers at onset with a higher reported frequency than in SLE, ranging from 55-98% (71-74, 76-79, 81-85, 87, 89, 91) in all manuscripts and 74-83% (77, 82, 84) in level 1b manuscripts. Finally, in IBD manuscripts, mouth ulcers at onset were reported in four ulcerative colitis manuscripts, eight Crohn's disease manuscripts and three unspecified IBD manuscripts. The frequency ranges for UC were 0-13% (93, 96, 102, 107), with 13% reported in one level 1b manuscript (96), for CD, were 3-30% (94, 96, 98, 99, 102, 107-109), with 5% reported in one level 1b manuscript, (96), and in unspecified IBD were 3-44% (102, 105, 107).

Overall, the studies demonstrate that mouth ulcers are more common at onset in Behcet's disease compared to SLE and IBD, although reported frequency ranges are large. SLE and IBD report similar frequencies of mouth ulcers at onset of the conditions, especially when focussing on level 1b evidence manuscripts.

Non-mouth ulcer symptoms were analysed in terms of the number of manuscripts a symptom category was reported in. In SLE the symptom categories that were most frequently reported across all manuscripts were joint involvement/arthritis, malar rash and renal involvement. For Behcet's disease these were genital ulcers, unspecified skin lesions and ocular involvement. Finally, in IBD these were abdominal pain, diarrhoea and perianal signs. The frequency ranges and number of reports are displayed in *Table 6.*

Table 6- Most frequently reported Symptom categories in terms of number of manuscripts, in SLE, Behcet's and IBD

	Symptom	**No. of manuscripts reported in**	**Frequency range**	**References**
SLE	*Joint involvement/ arthritis*	30	13-50%	(17-22, 24-35, 37-39, 41, 42, 44-46, 49, 53, 56)
	Malar rash	28	10-91%	(17-23, 25-28, 30-36, 38, 39, 41-47, 52)
	Renal involvement	27	2-86%	(17-23, 25-27, 29, 30, 35, 37-46, 49, 52, 53, 56)
Behcet's	*Genital ulcers*	13	2-69%	(71-74, 77-79, 81, 84, 85, 87, 89, 91)
	Skin lesions	9	4-82%	(71, 73, 77, 82, 84, 85, 87, 89, 91)
	Ocular involvement	9	2-27%	(71, 73, 74, 78, 83-85, 89, 91)
IBD	*Abdominal pain*	11	36-88%	(93-96, 98, 99, 102, 105, 107-109)
	Diarrhoea	10	26-71%	(93-96, 99, 102, 105, 107-109)
	Perianal signs	6	7-26%	(96, 98, 99, 102, 108, 109)

2.3.3 Time lag

The approximate time lag between onset of the condition (i.e. first symptom) and diagnosis was determined in SLE and Behcet's respectively, as included manuscripts in these conditions detailed age at onset and diagnosis plus symptoms at onset. These data points were available in three manuscripts for SLE. Mean age at onset ranged from 11-12 years and at diagnosis from 13-16 years (17, 19, 20). It can be calculated that the time lag between onset and diagnosis in this condition is 2-4 years.

In Behcet's disease, six manuscripts could be used to calculate time lag. Average (mean or median, whichever the manuscript reported) age at onset was 8-12 years, and at diagnosis was 12-14 years (77, 81-84, 89). So, the time lag between onset and diagnosis ranged from 3-4 years. There was a higher frequency of mouth ulcers at onset reported in these manuscripts compared to the three SLE manuscripts, namely 70-100% (77, 81-84, 89) compared to 9-14% (17, 19, 20). It could be hypothesised

that mouth ulcers could be used as a predicting factor prior to diagnosis, especially in Behcet's disease where the frequency is higher and time lag longer. This will be considered further in the Discussion (see *Section 2.4.1*).

2.3.4 Age

The data extracted from the included manuscripts was not sufficiently detailed to be used to determine the risk of systemic disease given the age at onset of mouth ulcers or other symptoms. However, it was possible to analyse the frequency of mouth ulcers at onset in relation to age at onset and diagnosis. The highest and lowest mean age reported at each time point was used and the frequency of mouth ulcers was compared. These results are presented in *Table 7*. No manuscripts for IBD reported age alongside symptoms at onset hence the missing data.

It is difficult to denote a trend between age at onset and mouth ulcer frequency in SLE and Behcet's since the highest and lowest values (of age for SLE and frequency of mouth ulcers for Behcet's) are too similar to compare. In all three conditions, the higher the age at diagnosis the lower the frequency of mouth ulcers reported at onset, when analysing retrospectively.

Table 7- Comparison of highest and lowest age at onset/ diagnosis with frequency of mouth ulcers at onset in each condition

		Highest mean age (yrs)	**Freq. mouth ulcers at onset (%)**	**Reference**	**Lowest mean age (yrs)**	**Freq. mouth ulcers at onset (%)**	**Reference**
SLE	*Onset*	12	14	(17)	11	37	(21)
	Diagnosis	18	3	(32)	8	22	(22)
Behcet's	*Onset*	13	70	(83)	8	74	(84)
	Diagnosis	15	55	(74)	9	77	(73)
IBD	*Onset*	-	-	-	-	-	-
	Diagnosis	14	5	(96)	9	30	(108)

Some manuscripts specifically divided their cohorts by age and compared the frequency of non- mouth ulcer symptoms, at onset, in the different groups. For example in SLE manuscripts: Chiang *et al* (21)

differentiated their cohort by pubescent status and found a significant difference in the frequency of renal symptoms/ nephritis. Zhu *et al* (24) split the cohort into pre-school, school age and adolescent and found a significantly higher frequency of arthritis in adolescents and hepatosplenomegaly in pre-school children. Gomes *et al* (29) noted a high frequency of fever, hepatomegaly, splenomegaly and discoid lupus in the <6 years old category whereas weight loss and photosensitivity were not as frequent in these children. No Behcet's manuscripts focussed on age and reported symptoms at onset. Two IBD manuscripts reported significant differences in symptoms in relation to age: Guariso *et al* (102) suggested many symptoms were significantly different in various age categories and that overall extraintestinal manifestations were lower in the 0-5 years category. In contrast, Gupta *et al* (99) reported higher rates of abdominal pain, weight loss and rectal bleeding in younger children. No manuscripts focussed on mouth ulcer frequency given the age at onset, however there is clearly a link between age and disease phenotype at onset that requires further investigation.

2.3.5 Sex

It was difficult to identify any differences between males and females in their risk of systemic disease diagnosis with the extracted data. However, it was possible to analyse the available manuscripts for potential trends in onset symptoms in relation to sex.

In SLE, 52 manuscripts reported sex with a female majority in all ranging from 68-98% (17-68). No SLE manuscripts specifically looked at the differences between males and females in terms of symptoms at onset of mouth ulcers, hence no conclusions could be drawn from the data without the risk of skew.

All Behcet's manuscripts reported sex, with a female frequency ranging from 25-63% (70-92). Only one Behcet's manuscript divided the study cohort by sex. However, symptoms at onset of the disease were not reported, the only difference in cumulative symptoms was reported in eye involvement (70).

Twenty one IBD manuscripts (91%) reported the sex distribution of their cohorts, with the frequency of females ranging from 12 to 66% (93, 95-102, 104-115). The only IBD manuscript reporting a significant difference in symptoms at onset when males and females were compared was Gupta *et al* (98). They reported a higher frequency of mouth ulcers at onset in the female cohort of their Crohn's disease population, with a frequency of 4% in girls compared to 1.4% in boys.

2.3.6 Ethnicity

Thirty four SLE manuscripts (17, 18, 21-26, 28-31, 33-43, 48, 50, 51, 54, 55, 57-61, 68) reported on ethnicity, with a Caucasian predominance in most (15 manuscripts (23, 25, 26, 29, 31, 33, 34, 36, 37,

51, 54, 57-60)), followed by Arab (four manuscripts (17, 35, 48, 50)) then Chinese (three manuscripts (18, 21, 24)) and Malay (three manuscripts (22, 30, 40)). *Table 8* shows the range of mean ages at onset and diagnosis, and the frequency ranges of the most commonly reported presenting symptoms in each ethnic predominance cohort. Manuscripts included in this table reported ethnicity and symptoms at onset. Despite being the second most common ethnic predominance, no manuscripts reporting Arab ethnicity cohorts also reported symptoms at onset. The highest frequency of mouth ulcers at onset was reported in Malay predominant cohorts. The highest burden of symptoms overall seemed to be in Chinese populations with malar rash particularly prominent, they also had the youngest mean age at onset.

One SLE manuscript (38) specifically reported on ethnicity in relation to symptoms at onset. A lower frequency of malar rash but higher frequency of serositis was reported in the Aboriginal/Black cohort; and a lower frequency of arthritis was reported in the Asian cohort. Both of these ethnic groups had a high frequency of renal involvement, compared to the other ethnic groups in this cohort: South Asian, Latino/Hispanic and White.

Table 8- Comparison of ages at onset/diagnosis and frequency of symptoms at onset in SLE manuscripts reporting different ethnic predominance

	Caucasian (*8)	**Chinese (*3)**	**Malay (*3)**
Range of frequency of ethnic predominance (%)	50-100 (*8)	100 (*3)	62-100 (*3)
Mean age at onset (yrs)	12.-13(*2)	11(*1)	NR
Mean age at diagnosis (yrs)	11-14 (*6)	13 (*1)	8-12 (*3)
Frequency of mouth ulcers (%)	3-36 (*8)	18-37 (*3)	22-49 (*3)
Frequency of joint involvement/arthritis (%)	22-67 (*6)	38-68 (*3)	13-44 (*2)
Frequency of malar rash (%)	11-60 (*7)	52-66 (*2)	28-52 (*2)
Frequency of renal involvement (%)	2-51(*4)	42-50 (*2)	40- 66 (*3)
References	(23, 25, 26, 29, 31, 33, 34, 36, 37)	(18, 21, 24)	(22, 30, 40)

NR= NOT REPORTED, (*)=NUMBER OF MANUSCRIPTS REPORTING

Eleven Behcet's manuscripts reported on the ethnicity of their cohorts, with a Turkish predominance in five (72, 75, 79, 81, 92), Caucasian in four (76, 77, 85, 86) and Japanese in one (73). The final

manuscript (84) reported equal thirds Caucasian European, Middle Eastern European and North African. None of these manuscripts analysed symptom variation at onset by ethnicity.

For the purposes of ethnicity comparison in this review, the ages and frequency of symptoms in the Turkish, Caucasian and Japanese predominance cohorts (with symptoms reported at onset) were analysed (*Table 9*). Age at diagnosis was lowest in the Japanese cohort and highest in the Turkish cohort. Age at onset was also highest in the Turkish cohort. The Japanese cohort had a higher frequency of children affected by genital ulcers than in both other ethnic predominance cohorts. They also had a higher frequency of skin lesions and ocular involvement prior to diagnosis, than the Caucasian cohort (the Turkish cohort studies did not report on these symptoms). The frequency of children affected by mouth ulcers at the onset of their Behcet's disease appeared similar in all ethnicities. However, the Turkish predominant cohort had a frequency range that was higher than the frequency in the Japanese cohort.

Table 9- Comparison of ages at onset/diagnosis and frequency of symptoms at onset in Behcet's manuscripts reporting different ethnic predominance

	Turkish (*3)	**Caucasian (*3)**	**Japanese (*1)**
Range of frequency of ethnic predominance (%)	100 (*3)	60-91 (*3)	100
Mean/ median age at onset (yrs)	12 (*1)	5-8 (*2)	NR
Mean age at diagnosis (yrs)	14 (*1)	12 (*1)	9
Frequency of mouth ulcers (%)	82-98 (*3)	74-90 (*3)	77
Frequency of genital ulcers (%)	2-4 (*3)	17-24 (*2)	45
Frequency of skin lesions (%)	NR	11-14 (*2)	39
Frequency of ocular involvement (%)	NR	2(*1)	10
References	(72, 79, 81)	(76, 77, 85)	(73)

NR= NOT REPORTED, (*)= NUMBER OF MANUSCRIPTS REPORTING

Eleven manuscripts reported ethnicity in IBD cohorts, with Caucasian predominance in six (93, 96, 98-100, 106) and Chinese predominance in five (105, 108, 110, 112, 114). *Table 10* compares manuscripts reporting symptoms at onset and either Chinese or Caucasian predominance in the cohort. The age at IBD diagnosis was lower in the Chinese predominant cohort compared to the Caucasian predominant cohort. In terms of symptoms at onset, the frequency of mouth ulcers, diarrhoea and perianal involvement were greater in the Chinese predominant cohort. The frequency of abdominal pain at

onset was similar in the two groups. No IBD manuscripts analysed symptom variation at onset by ethnicity.

Table 10- Comparison of ages at onset/ diagnosis and frequency of symptoms at onset in IBD manuscripts reporting different ethnic

	Caucasian (*4)	**Chinese (*2)**
Range of frequency of ethnic predominance (%)	80-93 (*4)	50-100 (*2)
Mean/ median age at onset (yrs)	NR	NR
Mean age at diagnosis (yrs)	11.5-13.5 (*4)	9.4-10.8 (*2)
Frequency of mouth ulcers (%)	2.3-5 (*4)	30-43.8 (*2)
Frequency of abdominal pain (%)	41.7-86 (*4)	55-87.5 (*2)
Frequency of diarrhoea (%)	30-93 (*3)	70-75 (*2)
Frequency of perianal involvement (%)	7.2-15 (*3)	25 (*1)
References	(93, 96, 98, 99)	(105, 108)

NR= NOT REPORTED, (*)= NUMBER OF MANUSCRIPTS REPORTING

2.3.7 Access to healthcare

No manuscripts included in this literature review detailed patients' journeys prior to the point of referral to specialist care, i.e. there were no manuscripts reporting solely primary care data. Most manuscripts, within all three conditions, reported data from tertiary care centres with the majority being outpatient clinics. Various specialties were noted to have input into care: in SLE and Behcet's this was predominantly rheumatology and nephrology with some additional support from haematology in SLE and ophthalmology in Behcet's, whereas IBD patients utilised gastroenterology, dental and oral medicine.

2.3.8 Other conditions

Other conditions that present with mouth ulcers also appeared in the database search results and met the inclusion criteria of this review. There were 21 manuscripts referencing coeliac disease (116-136), 18 manuscripts referencing periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA) syndrome (137-154), three on familial Mediterranean fever (FMF) (153-155), and one on each of recurrent aphthous stomatitis (RAS) (133), eosinophilic colitis (156), TNF-α Receptor-Associated Periodic Syndrome (TRAPS) (157) and hand, foot and mouth disease (158) respectively. Detailed analyses and consideration of the data arising from these was beyond the scope of this present study.

2.4 Discussion

2.4.1 Mouth ulcers

The results of this review indicate that, at onset, mouth ulcers are most common in Behcet's disease: a range of 55-98% (56-59, 61-64, 66-70, 72, 74, 76) compared to 3-74% (2-18, 20, 21, 23-32, 34, 37, 38) in SLE and 0-44% (78, 79, 81, 83, 84, 87, 90, 92-94) in IBD generally. This difference is amplified in the level 1b evidence manuscripts with a range of 74-83% (62, 67, 69) in Behcet's compared to 3-21% (3-5, 12, 17) in SLE (no IBD manuscripts reporting onset symptoms were considered to be level 1b evidence). Behcet's disease was also the condition with the most patients with mouth ulcers cumulatively: a range of 95-100% (55-61, 63-66, 68-71, 73, 75-77) in all manuscripts reporting at this timeframe with level 1b manuscripts reporting 100% (144) at the cumulative time point. This is compared to the SLE range of 4-78% (2-5, 8, 12, 13, 19, 21, 22, 32, 33, 35, 36, 40-52, 54), with 1b manuscripts reporting 20-49% frequency (3-5, 12, 18, 19, 36, 39, 40) and when compared to that reported in IBD manuscripts which ranged between 0-87% (78, 80, 82, 85, 86, 88, 89, 91, 95-100), with 1b manuscripts reporting a range of 7-34% (80, 82, 85, 95-97, 99).

These data are in line with current understanding of each of the conditions, particularly the accepted international classification criteria for each of them. in the UK. For IBD, neither the Montreal nor Paris classification criteria, recommended for use by the British Society of Gastroenterology, mention mouth ulcers as a diagnostic sign for Crohn's or UC (145). The 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (146), as recommended for use in children by the 2017 Single Hub and Access point for paediatric Rheumatology in Europe (SHARE) recommendations (147), include 'mouth ulcers' as one of many criteria. Petri *et al* (146) states a 92.1% specificity for mouth ulcers in SLE within the SLICC criteria when compared to CYP with other rheumatological conditions, meaning mouth ulcers are not always indicative of SLE. However, all diagnostic criteria for Behcet's disease, in practice, include mouth ulcers as a key feature. For example, in the International Criteria for Behcet's Disease (ICBD), oral aphthosis are assigned 2 points with a reported sensitivity of 98% (148). Additionally, the International Study Group (ISG) criteria requires all patients to have recurrent mouth ulcers, so studies using ISG as inclusion criteria will always have 100% of patients with mouth ulcers (149).

Many of the included IBD manuscripts reporting cumulative frequency of mouth ulcers, focussed on extraintestinal manifestations (EIMs), hence the reported frequency range in this review may be an overestimation in terms of the general paediatric IBD population. Other cumulative symptoms not related to the intestine, as described in this review, could also report overestimated frequencies given the methodology of some of these manuscripts.

Zhou *et al* (95) was the only manuscript reporting solely cumulative frequency of symptoms that did not focus on EIM. They clinically and radiographically examined any children with suspected IBD at one hospital, hence their cumulative frequency of 25% mouth ulcers may be the most accurate figure in this review in terms of the general IBD population. This manuscript (95) also presents data that agrees with the accepted trend that mouth ulcers are more common in Crohn's patients when compared to UC patients (20% vs 13% cumulatively in this manuscript). Due to this known association and this review categorising UC and CD patients together, the frequencies of mouth ulcers presented for the IBD cohort may be overestimations in terms of paediatric UC populations specifically.

2.4.2 Presenting symptoms

Non-mouth ulcer presenting features were not consistent across manuscripts or conditions and hence collating the frequency of reported symptoms proved challenging. It was decided to initially assess symptoms based on the number of manuscripts that they were reported in, since this represented the manuscripts in their entirety. It was not assumed that they were the most common in frequency among patient cohorts, merely that more investigators deemed them significant enough to report. The frequency ranges were reported alongside symptom categories. However, these were large and hence a valid trend could not be derived.

The most common symptoms in each condition have been summarised in *Table 6*. Most of these common symptoms can easily be noted by primary care physicians in order to determine risk of systemic disease given mouth ulcers. For example: arthritis, malar rash and renal involvement in SLE; genital ulcers and skin symptoms in Behcet's; and abdominal pain, diarrhoea and perianal signs in IBD. The only sign that would not be assessed in a primary care facility would be ocular involvement in Behcet's which can be silent and would need ophthalmology review. These triads of symptoms, when presenting alongside mouth ulcers in children, could be used as a simple tool by primary care physicians to indicate the need to refer to tertiary care to consider evolving systemic disease.

2.4.3 Time lag

The time delay between onset of symptoms and diagnosis could only be determined in SLE and Behcet's, but was limited by a paucity of data including three studies for SLE and six for Behcet's. In SLE the time lag was calculated at 2-4 years (2, 4, 5), and in Behcet's it was possibly longer at 3-4 yrs (62, 66-69, 74). The frequency of mouth ulcers at onset in each condition was discrepant, 9-14% (2, 4, 5) in SLE vs 70-100% (62, 66-69, 74) in Behcet's, hence it could not be inferred that the time lag was

between onset of mouth ulcers specifically and diagnosis. The time lag data in relation to mouth ulcers is more valid in Behcet's disease as there were more manuscripts able to contribute data (62, 66-69, 74). However other published literature, not included in this review, reports an average of 6 to 7 years between mouth ulcers and occurrence of a second symptom (160, 161), before a diagnosis is even considered. One of the studies contributing data to this figure selected patients based on the presence of recurrent oral ulceration and no other risk factors for Behcet's disease. The other manuscript focussed on solely joint manifestations as the 'second symptom'. These variations in methodology may explain the discrepancy in time lag data between these studies and this review. Further study is required, with uniform methodology including non-restrictive selection criteria and robust follow up protocol, to decipher the true time lag between mouth ulcers and diagnosis in all three conditions.

2.4.4 Age

The age definition of childhood-onset was not stipulated specifically in this systematic review. There were differences within the studies reviewed in terms of upper age limit for 'childhood' as it is not universally determined. The accepted age for disease onset ranged from less than 2 years (infantile-onset IBD) (150) to less than 21 years (65, 73). In future systematic reviews it may be beneficial to limit manuscripts to a set definition of childhood-onset (i.e. <18 years at onset of symptoms) however this was not implemented in this review because the aim was to collect as much evidence as possible since this is the first systematic review relating to this question. This restriction would have excluded key manuscripts with large cohorts and useful data, such as both Behcet's manuscripts by Davatchi *et al* (65, 73) with 4,341 cases total, which had an upper age limit for onset of symptoms of 21 years.

In terms of symptoms, the frequency of mouth ulcers at onset decreased as age at diagnosis increased (2, 6, 7, 17, 58, 59, 68, 69, 81, 93). Generally, it is understood that peak incidence of mouth ulcers in the general paediatric population occurs at 10-19 years (151) which would be the older portion of the population in this review. Hence it could be hypothesised that mouth ulcer frequency at diagnosis would be higher in the older age category, which would contradict the results of this review. More research is required to determine if this peak incidence is true in these 3 conditions specifically and hence resolve the discrepancy. Especially since it was not possible to denote a trend between age at onset of disease and the frequency of mouth ulcers at onset since relevant/ comparable data was not available.

2.4.5 Sex

As no included SLE manuscripts analysed symptoms at onset based on sex, we were unable to determine the phenotypic differences in presentation of SLE in males and females. As in SLE, no Behcet's manuscripts reported symptoms at onset in terms of sex. One manuscript (55) reported a significant finding in eye involvement frequency cumulatively when males and females of this cohort were compared.

In IBD manuscripts Gupta *et al* (83) was the only manuscript to report a significant difference in symptoms at onset when males and females were compared. They reported a higher frequency of mouth ulcers in the female cohort of their Crohn's disease population. Future studies may be able to verify if females are more prone to mouth ulcers in UC, as well as Behcet's and SLE.

The paucity of results in terms of sex comparison highlight the requirement for further study of this area in all 3 conditions.

2.4.6 Ethnicity

In terms of ethnicity, most manuscripts reported frequencies of ethnic groups that reflected the population of the country in which the study was conducted. However, some SLE manuscripts restricted cohorts based on ethnicity (for example Arab, Korean, Egyptian, Kuwaiti, Filipino, Chinese etc.) and hence the data was not reflective of the general population in these cases (3, 6, 13, 20, 24, 33, 35, 46). Overall, there was a wide spread of ethnicities throughout the conditions and manuscripts and the data sources reflect the international perspectives on ethnic distribution.

It is known that white Caucasian children are at relatively lower risk of developing SLE (152). Hence, it could be hypothesised that the available literature included in this review misrepresents the condition, since more manuscripts reported Caucasian predominance than any other ethnicity. However, this could be due to unreported ethnicity data, or this review being conducted using manuscripts only published in English. It was found that in SLE, Malay predominant cohorts had the highest frequency of mouth ulcers at onset (7, 15, 25). Chinese populations had lowest onset age and the highest symptom burden overall, with malar rash frequency at onset high (3, 6, 9). It is difficult to compare ethnic variation in presentation characteristics since ethnicity was defined differently in various studies. Furthermore, the large symptom frequency ranges produced by this review adds to the complication of comparing results to what is known at present.

It is widely accepted that Behcet's disease affects more children from ethnicities along the historical Silk Route (Northern China, Iran, Turkey, Turkish German population) (144). Turkish/ German

predominance was reported in over half of manuscripts reporting ethnicity (57, 60, 61, 64, 66, 77), hence it can be concluded that the cohorts included in this review are somewhat reflective of the known Behcet's population in terms of ethnicity.

In Behcet's manuscripts, the Japanese cohort had a higher frequency of children affected by genital ulcers, skin lesions and ocular involvement at onset, and a lower mean age at this time point (58). Current literature would agree that Japanese children are more commonly affected by ocular involvement, specifically uveitis (153), however it is generally thought that Caucasian children would have a higher prevalence of genital ulcers (154). The only symptom that did not seem to be affected by ethnicity was mouth ulcers. This finding could have been due to the criteria used in the analysed studies: ISG criteria (149) was used in the Caucasian and Turkish predominant cohorts (57, 61, 62, 64, 66, 70) whereas the Japanese Criteria for the diagnosis of Behcet's Disease (155) was used in the Japanese predominant cohort (58). ISG criteria requires mouth ulcers for diagnosis whereas the Japanese criteria does not, hence the frequency could have been skewed in the Caucasian predominant cohort when compared with the Japanese cohort. Also, this comparison was difficult given that the ethnic predominance in the Japanese and Turkish cohorts was 100% (57, 58, 64, 66), but only 60 to 91% (61, 62, 70) in the Caucasian cohorts hence the frequency figures may have been skewed by other ethnic groups included in these studies.

There is limited data on ethnic variation in paediatric IBD but it is thought that in the UK, IBD is more common in children of Asian ethnicity (156). In terms of findings reported in this review, Chinese children had a lower age at diagnosis and higher frequency of mouth ulcers, diarrhoea and perianal involvement at onset (90, 93). The frequency of abdominal pain at onset did not show significant ethnic variation.

Due to the different ethnic predominance and symptoms evaluated in this review, we are not able to compare the ethnic variation between the 3 conditions.

2.4.7 Access to healthcare

All manuscripts in this review were focussed on patients in a tertiary care setting and there are very limited data currently available regarding paediatric systemic disease in primary care. Caution should therefore be taken when applying these results to a primary care population.

2.4.8 Disease classification

The classification criteria used to define each disease was also not universally identified, and this was exaggerated by the broad time and geographical span of the included manuscripts. This may have led to selection bias within each study as some criteria are stricter than others. In future reviews the inclusion criteria could define the acceptable classification system. For example, the most commonly used for each condition from this review: American College of Rheumatology (ACR) classification in SLE; ISG criteria in Behcet's'; and clinical evaluation in IBD. However, this may lead to manuscript selection bias within the review as some countries will have nationally accepted classification systems that do not match the inclusion criteria. These will be excluded and hence some ethnicities may be excluded resulting in an ethnic bias due to limited representation.

This approach would also have excluded a lot of data in this review, on an already scarcely reported topic. For example, the Behcet's ISG criteria requires recurrent mouth ulcers to be fulfilled (149) hence inclusion would mandate 100% cumulative mouth ulcers, considering only 13 Behcet's manuscripts reported this figure (55-59, 61, 63, 64, 66, 68, 69, 76, 77), almost half of the symptom data presented in this review would have been lost.

2.4.9 Timeframes

The discrepancies between manuscripts as to what time points symptoms were reported at (i.e. onset, diagnosis, cumulative, follow up etc.) led to difficulties in data analysis as results were not always directly comparable. It was decided that manuscripts with a variety of time frames were to be included since useful symptom frequency data was available from all. In future work, manuscripts with a sole time frame (e.g. symptoms at onset only) could be evaluated in a more thorough manner.

2.4.10 Study designs

Most manuscripts across all conditions were rated as level 2b evidence: retrospective, observational cohort studies. Other included study designs are listed in *Table 4*. This may affect the validity of the results of this review in a number of ways.

Due to the retrospective nature of these studies, there is a greater risk of selection bias. This could be because patients with a systemic disease diagnosis are more likely to have intact health care records and more frequent healthcare contacts than healthy individuals, and are therefore less likely to be lost to follow up. Furthermore, the more severe/ symptomatic cases are again more likely to have more complete records due to the nature of the care they require. Selection bias could have been

reduced in these studies by comparing the baseline characteristics of patients lost to follow up (i.e. did not have intact records when retrospectively reviewed) with those that completed the study, or by having rigorous protocol on the selection of cases and controls. Also controls with other conditions not related to mouth ulcers may have been more appropriate, as they will have had similarly increased healthcare contacts and complete records.

Another form of bias that can be introduced through retrospective study design is recall bias. Most studies looked at past medical records which is less prone to this bias, however if records were unclear or clarification was required it may have still been introduced. Some studies used questionnaires to collect data on past symptoms (i.e. at the onset of the condition), this method of data collection is prone to recall bias especially if children themselves were asked to recall symptoms from years prior. The effect of this bias could be reduced if the study design selected subjects with equal tendency to recall facts (i.e. always ask parents despite the age of the child). To try and eliminate this bias, nested case-control design may have been a more appropriate investigative technique and verifying collected data using pre-existing records should have been completed where possible.

The risk of confounding is another issue in retrospective, observational cohort studies, as the data was originally collected for other purposes such as medical record keeping. Hence not all relevant information may have been available for analysis. There are various ways in which this could have been reduced in the study design process. Firstly, if cohorts had been restricted by the possible confounders for example age or sex, these factors would be eliminated from affecting the results. However, implementing this can significantly restrict the application of results to wider populations, also in our case of a systematic review would have affected a study's accurate comparability to other studies. The study design could have also matched cases and controls by various confounders (e.g. age/sex), which would reduce their impact. But, as with restriction, the effect of the variable used for matching cannot be evaluated.

Alterations to the statistical analysis could have assisted in reducing the risk of confounding further. For example, stratification would have allowed various subset analyses, however this would have also reduced the power to detect effects. Regression analysis could have been applied to compare adjusted and unadjusted estimates of effect size, if these were shown to differ greatly it would be concluded that baseline characteristics were a source of confounding that significantly affected outcomes.

Despite the limitations of the level 2b evidence study designs, lack of a more rigorous evidence base determined that these should be included them in this review. Since no systematic review relating to our specific question has been completed prior to this, it was deemed important to collate as much data as possible on the topic. Furthermore, these manuscripts contained important data that

contributes to our understanding of the review question. The effect of the aforementioned bias and confounding risks does not seem to have distorted the results compared to level 1b evidence manuscripts. For example, in our main outcome of mouth ulcers at onset, the average frequency in Behcet's disease was 84% for level 2b evidence manuscripts (56-59, 61, 63, 64, 66, 68, 70, 72, 74, 76), and 79% in level 1b evidence manuscripts (62, 67, 69).

2.4.11 Prospective, Longitudinal Cohort study

Since the studies included in this review were not sufficiently homogenous in terms of study design, subjects and outcome measures, a meta-analysis could not be performed to confirm these results. A large prospective, longitudinal cohort study should ideally be performed to assess the presence of mouth ulcers in children, prior to a diagnosis of each of these conditions, for valid comparisons to be made. Although a prospective cohort study would be able to analyse the conditions in a wider context, there would be many challenges associated with conducting it, not least the risk that it could be subject to selection bias and loss to follow up.

Such a proposed prospective cohort study would also have the ability to produce valid conclusions in comparing these conditions. It could assess the issue in the context of primary care using all available patient records but would be limited by variation in health seeking behaviours and valid record keeping. This review has raised a series of questions which should be satisfied by the results of such a cohort study.

Firstly, the most common non-mouth ulcer symptoms at presentation could be analysed further, to determine if the use of certain symptoms as precursor signs, when presenting alongside mouth ulcers, is supported by primary care data. Furthermore, the study will assess the risk of systemic disease given age at onset of mouth ulcers, as opposed to the risk of previous mouth ulcers given age at onset/diagnosis (as in the included studies of this review), since this holds more clinical relevance.

The results of the cohort study would be able to be adjusted and stratified by age, sex and ethnicity hence evaluating the variation of SLE, Behcet's and IBD by these factors: a requirement highlighted by this review. Since a cohort study would be able to assess primary care records, the study will address the gap in literature around access to healthcare, identified in this review. Such a focus would be on patients at the beginning of their journey with a systemic condition, as this may be a key area for effective clinical intervention.

2.4.12 Limitations of the systematic review methodology

The main limitation of this systematic review was the search strategy that excluded manuscripts which were not written in the English language, hence introducing a selection bias. The risk of this bias is that manuscripts detailing patients from certain regions/ethnicities may have been excluded, and hence there is potential for an ethnic skew in the findings of this review. Future systematic reviews on this topic should assess manuscripts written in non-English languages to compare with the findings of this study.

Furthermore, the definition of diagnosis for each disease was accepted as stated in each manuscript. However, manuscripts used various diagnostic/ classification criteria and hence there was not a universal criterion for diagnosis in this review. Hence some manuscripts may not be comparable in certain aspects, for example age at diagnosis or time lag from first symptom to diagnosis. In future systematic reviews it may be possible to use a universal definition of diagnosis by retrospectively analysing raw symptom data. This may be affected by data availability as well as reporting behaviours of research teams.

2.5 Key findings

This systematic review has highlighted the follow important findings:

- No current published literature assesses the risk of systemic disease, specifically SLE, Behcet's or IBD, in children who present to a healthcare setting with mouth ulcers.
- Further research is required to determine if the most common non-mouth ulcer symptoms at presentation, formulated in this review, are applicable to a primary care setting.
- There is generally a delay between onset of systemic disease and diagnosis. However, the presentation at onset and clinical relevance of the delay requires further investigation, particularly with regards to the symptom of mouth ulcers.
- Age has a variable association with mouth ulcers when the conditions are compared; risk stratification by age for specific symptoms as well as for overall diagnosis in each condition would determine if these conclusions were valid.
- There are sex and ethnic variations in phenotypic presentation of systemic disease that require further analysis, specifically how these contribute to cumulative risk of systemic disease.
- More literature is required to assess this issue in a primary care setting as compared to solely tertiary care.

2.6 Conclusions

Overall, this systematic review has demonstrated that there is currently no available literature to specifically answer the review question: *'Are children who present to a healthcare setting with mouth ulcers at an increased risk of developing a systemic disease, specifically SLE, Behcet's or IBD?'*

Collection of data on the symptoms that each of these conditions present with, including mouth ulcers, was not able to be determined. Future research needs to be done to establish a quantitative risk of progression from mouth ulcers to systemic disease in childhood. The CPRD cohort study undertaken as part of this project (see Chapter 4) will seek to address some of these challenges.

3 Chapter 3: Patient and Public Involvement: Views and Insights

3.1 Introduction

Patient and public involvement and engagement (PPIE) should be a key consideration when conducting any type of healthcare research. All stages of research can benefit from PPIE, for example formulation of research priorities and aims, input into the development of proposals, as well as ideas around delivery and dissemination. It is important to consider the views of patients and the public as they may differ from that of the research team, there is an opportunity to gain a different perspective on the which aspects of the work are most important that may not have been previously considered. The quality of any research will be improved by considering all views, and input from patients throughout the study ensures confidence in the final results. A patient is one of the best-informed members of the team for their condition, and hence it is vital that their opinion on research into the condition is heard.

PPIE is particularly important in research focussing on paediatric populations. Patients' views can often be overlooked because of their age, which does an injustice to the lived experiences and insights of CYP. It is also important to understand the views of parents/carers since conditions affecting CYP have a wider impact on the whole family due to caring responsibilities.

This chapter summarises the PPIE input and insights contributing to this project and involved both patients and parents with experience of all three conditions. They were asked to input and consider specific aspects assessed in the CPRD cohort study (SLE, IBD and Behcet's), as well as familiarity and first-hand experience in healthcare settings and the diagnostic journey in general.

There were three phases of the PPIE-focussed study which each contributed to the overall aim of tailoring the research to the patients and families it is hoping to help, as well as addressing individual aims. Details of the phases and aims can be seen in *Figure 2*. These individual aims were:

1. An initial meeting to establish important outcomes and language to be used in the project as a whole.
2. An online survey involving three groups of participants (SLE, IBD and Behcet's) to gain further insight into the perception of proposed outcomes and language from both patients and parents.
3. Meeting with CYP involved with YourRheum (a young person's advisory group) to discuss the results of the CPRD cohort study in terms of acceptability and dissemination of the findings.

3.2 Methodology

There was a multiphase approach to collecting opinions in this study: each phase informed the next, as well as collating to inform the CPRD study.

The first phase consisted of an initial meeting with young people who had experience of healthcare in general. The aim of this was to explain the project and collect their views on important aspects such as outcomes and language. The results of this phase informed three surveys adapted for each condition (SLE, IBD and Behcet's) that asked similar questions to the first phase however with response informed adaptations and in greater depth. The surveys were sent to various relevant charities and patient/parent groups covering all three systemic diseases. These two phases combined allowed the CPRD study to be tailored to the requirements and wishes of the people that the study was aiming to benefit. The final phase of the PPIE input was in the form of a meeting with young people who had experience of rheumatic conditions. This was with the aim to share the findings of the study as well as understand the views, of young people around the findings and how to disseminate the results. A three-phased approach was selected in order to collate a suitable breadth and depth of opinions relating to the CPRD cohort study.

Details of each phase are presented in *Figure 2*.

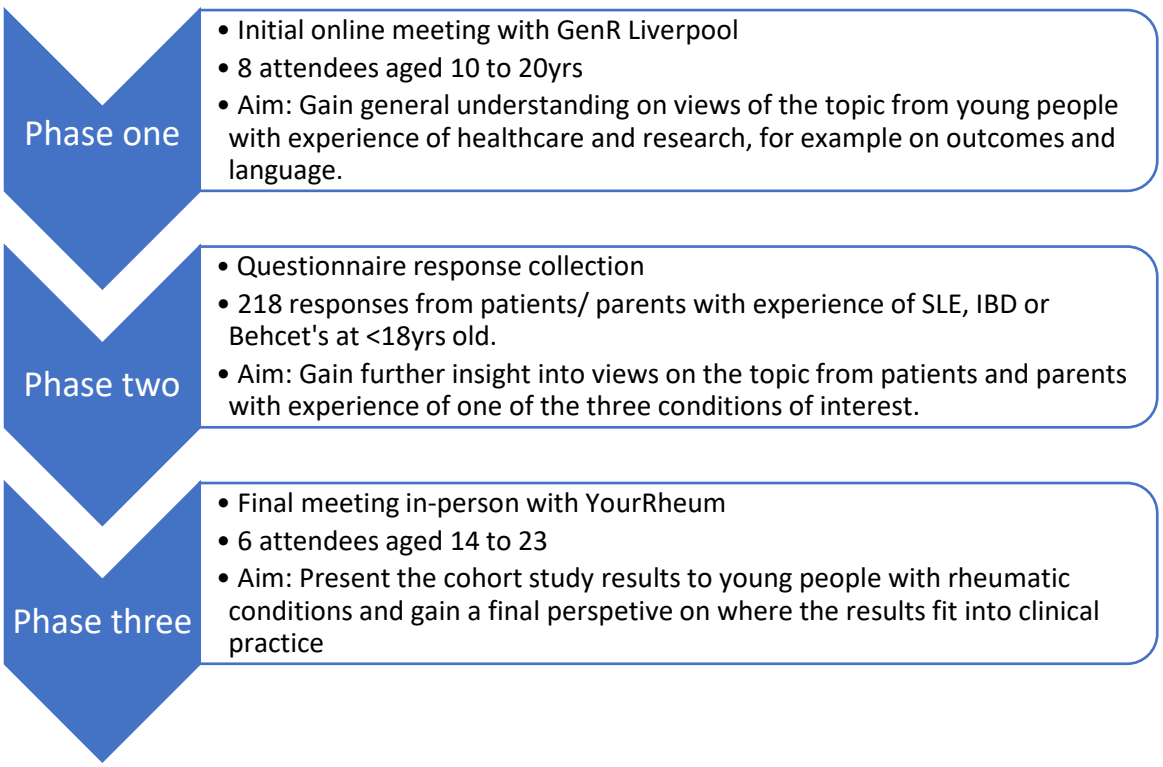

Figure 2- Flow diagram detailing the multiphase approach to collating PPIE input on the CPRD cohort study

3.2.1 Phase one: Initial meeting

Facilitated via the Youth & Family Participation Officer for the UK's Experimental Arthritis Treatment Centre for Children (EATC4C: https://www.liverpool.ac.uk/eatc-for-children/), the initial meeting was with the Generation R Young Persons Advisory Group (YPAG) in Liverpool. They are a group of young people aged between 9 and 21 who have taken part in health research or live with a condition or disability (not specifically rheumatic conditions or one of the three systemic diseases). The group is a space for the members to discuss with researchers and give their insights on, numerous aspects of paediatric research and clinical trials, this can aid researchers in enhancing their health research in terms of development and distribution.

Prior to meeting with the young people, the facilitator was consulted regarding the ages/development of the expected attendees and hence the appropriate content and level of information to be included. It was agreed that the meeting would include approximately 10 young people ranging in age from 10 to 21 years, as well as the facilitator and researcher, and would last approximately 45 minutes via Zoom. An animated presentation was created to be used as a visual aid to facilitate the discussion topics. The main themes of discussion were planned to cover proposed outcomes and language. Overall, the aim of this meeting was to gauge general opinion of the study and allow the young people to express their views prior to the study being finalised.

In order to become a member of Gen R Liverpool, the young people and their parents must sign a consent form which agrees to their participation and for any views expressed to be used by researchers, hence ethical approval was not required for this activity.

3.2.2 Phase two: Patient Surveys

Informed by the discussions of the initial meeting, three surveys were created with similar themes to the meeting discussions. The aim of this phase was to collect a larger sample of opinions on the study, from more targeted participants (i.e. patients/ parents with experience of the systemic diseases of interest). The surveys were created online in the Qualtrics software since it was deemed that an anonymous link was the fastest and most accessible method to distribute the surveys and collate responses. They consisted of an information sheet detailing the study and the survey, followed by 10 questions, and finally an additional comment box. Each survey asked the same questions of its respondents, the phrasing of the questions however was tailored to each of the three systemic diseases of interest. An example of the survey for patients/ parents with experience of SLE is show in *Appendix B*.

Prior to distribution, the phrasing and format of the questions were modified in collaboration with a patient volunteer from Lupus UK, to ensure they were easily understandable and would provoke the type of responses that would be beneficial in informing the research. For example, eliminating medical jargon, giving examples to aid understanding and limiting the number of free text boxes for answers.

Criteria for participation were: patients or parents of patients who had experienced symptoms of their systemic disease at less than 18 years old. It was decided that 18 years be the upper age limit for the surveys, despite it being 16 in the study, since the groups that distributed the surveys included young people up until the age of 18 years. The first few questions of the survey confirmed that the respondent met the participation criteria and asked if they had experience of key exposure of the study: mouth ulcers.

The anonymous link to each survey was distributed by various organisations involved with each condition: Lupus UK (https://www.lupusuk.org.uk/), Crohn's and Colitis UK (https://crohnsandcolitis.org.uk/), and Behcet's UK (https://behcetsuk.org/). Distribution was primarily via social media, with some targeted circulation in mailing lists and support groups. The links remained live for a minimum of one month in order to collect a sufficient sample of responses prior to the finalisation of the CPRD study.

The University of Liverpool research ethics team were consulted prior to distribution, and it was deemed that since the surveys were PPIE activity, ethics committee approval was not required so long as principles such as consent and confidentiality were maintained. It was suggested that review may be sought if this work was to be published for the purpose of completeness.

3.2.3 Phase three: Final follow-up meeting with CYP

Once the cohort study had produced results, a meeting was arranged with YourRheum (https://yourrheum.org/), in order to receive feedback from young people on the findings. YourRheum is a national organisation for young people aged 11 to 24 years diagnosed with rheumatic conditions, who can advise, input and shape current paediatric rheumatology research. At present, there are 44 active members meeting regularly in various capacities. It was believed that this group would give the most insightful perspective on the relevance and acceptability of the results, since the young people involved have lived experience of rheumatological diagnoses.

A face-to-face meeting was planned, and an open invite was circulated to members, no restrictions were put on the diagnoses of attendees as it was felt a variety of perspectives would be beneficial. Results were presented to the attendees in a developmentally appropriate format, and any confusion

was discussed and resolved. The summary of results given to the group was that CYP who attend their GP with mouth ulcers have a higher chance of receiving a subsequent systemic disease diagnosis.

Once an initial, open discussion had concluded, three key themes were introduced in order to focus and clarify thoughts: helpfulness, emotions and communication. A discussion around the helpfulness of the results was conducted with the group as a whole, with common scenarios presented to the YP. For example, mock exam results and traffic jams were the initial scenarios which helped put the results of this study into context and allowed the attendees to assess the helpfulness of the findings.

An activity was then commenced around each of the two remaining themes and the YP were encouraged to discuss their opinions on each prompt. In the 'emotions' theme the YP were asked to consider how they or their parents may have felt if given the results of this study in the context of their own diagnosis journey. Whereas in the 'communication' theme they were asked to consider the practicalities of communicating these results: Who should be told? Who is in the best position to deliver the results? And what additional information should be given alongside the results? Discussions were captured via written ideas on activity sheets, as well as notes taken by facilitators and the researcher.

3.3 Results

3.3.1 Phase one: Initial meeting

Eight GenR Liverpool members attended the online meeting, ranging in age from 10 to 20 years old, with an even distribution of males and females. The main findings of all discussions in the meeting can be seen in *Box 1.*

Box 1- Main findings from initial meeting

Outcomes

- *Reassuring/ empowering to know the risk.*
- *Must be a balance between 'realistic and scary' when communicating risk.*
- *Risk should only be given if there is that action can be taken.*

Language

- *All language used should be explained prior to use.*
- *'Mouth ulcers' and 'systemic disease' were both acceptable terms.*
- *'Risk' was the most preferred term to communicate the proposed outcome of the study.*
- *'Young people' was the most preferred term for patients in the study.*

3.3.1.1 Outcomes

The first discussion surrounding the planned outcome of the study (i.e. quantifying the risk of systemic disease in children who present to primary care with mouth ulcers) produced three main topics of opinion.

Firstly, most attendees agreed it would be reassuring/ empowering to know the risk so that they could be informed about red flag symptoms and take control of their own health, they felt if the risk was there then they would rather know about it so they can be informed prior to a diagnosis.

The second topic raised was about the 'balance between realistic and scary' when talking about risk, particularly with younger children. It was agreed that the depth of the conversation should depend on the age of the patient and that younger children should be separate from conversations had with their parents about risk. There was split opinion on whether it is helpful to know possibilities or whether it was daunting to be given so much information so soon, it was agreed that there was a balance to be struck.

Finally, there were comments made about the risk of systemic disease not being given to patients/parents unless there was something actionable included in the conversation. For example: many attendees queried if earlier intervention was possible given the known risk; there were also suggestions that contacts for support groups or helplines for the 'at risk' condition be provided at an appointment early in the diagnostic journey; or that informed conversations about future treatment options may be reassuring. Some attendees felt that if the risk was inevitable, and there was no

possibility of earlier intervention, then there was no point in knowing because the knowledge would induce worry. Others felt that knowing the risk would be good preparation even if the diagnosis was inevitable, on the provision that accurate sources of information be provided to the patient/ parent: there was agreement that unsupervised online searches for any condition would be scary.

3.3.1.2 Language

The second topic of discussion related to the language that would be acceptable to YP, in the written manuscript of the study or patient friendly leaflet of results for example. The conclusions arising from this discussion was that if any language used was explained thoroughly before its use, then most phrases would be acceptable.

The attendees were keen to reiterate that young people should always be offered an explanation as well as their parents. The first phrase discussed was 'mouth ulcers'. The attendees did not foresee any issues with the use of this phrase although a simple description at the start of any literature would ensure clarity. Secondly the term 'systemic disease' was deemed a good phrase to describe the three conditions so long as it was explained as it had been to them: a condition that can affect the whole body. Finally, there was a longer discussion around the word 'risk' in this context. Some attendees agreed with the use of this word as it showed it can be avoided (it is not necessarily inevitable) but that it should also 'not be taken lightly'. They felt that it struck the right balance between 'realistic' and 'scary' that had previously been discussed. Alternative terms discussed were 'chance' which was deemed to 'water down' the issue, and 'susceptibility', which was considered acceptable but 'risk' was easier to understand.

A final discussion confirmed how the attendees would like to be referred to if they were the focus of this study. 'Young people' was deemed most preferable, whereas 'teenagers' was not 'scientific' enough and 'adolescents' was associated with negative stereotypes such as 'moody and lazy'.

3.3.2 Phase two: Patient Surveys

The number of responses to the surveys varied by condition. Overall, there were 218 responses: 108 in IBD, 95 in Behcet's and 15 in SLE. In all conditions, the majority of responses were from patients themselves rather than their parents/ carers: 54% patient responses in IBD, 81% in Behcet's and 93% in SLE. Most respondents stated that they/ their child had experienced mouth ulcers at some point in their disease course, ranging from 81-96% of respondents. These responses are displayed in *Figure 3*.

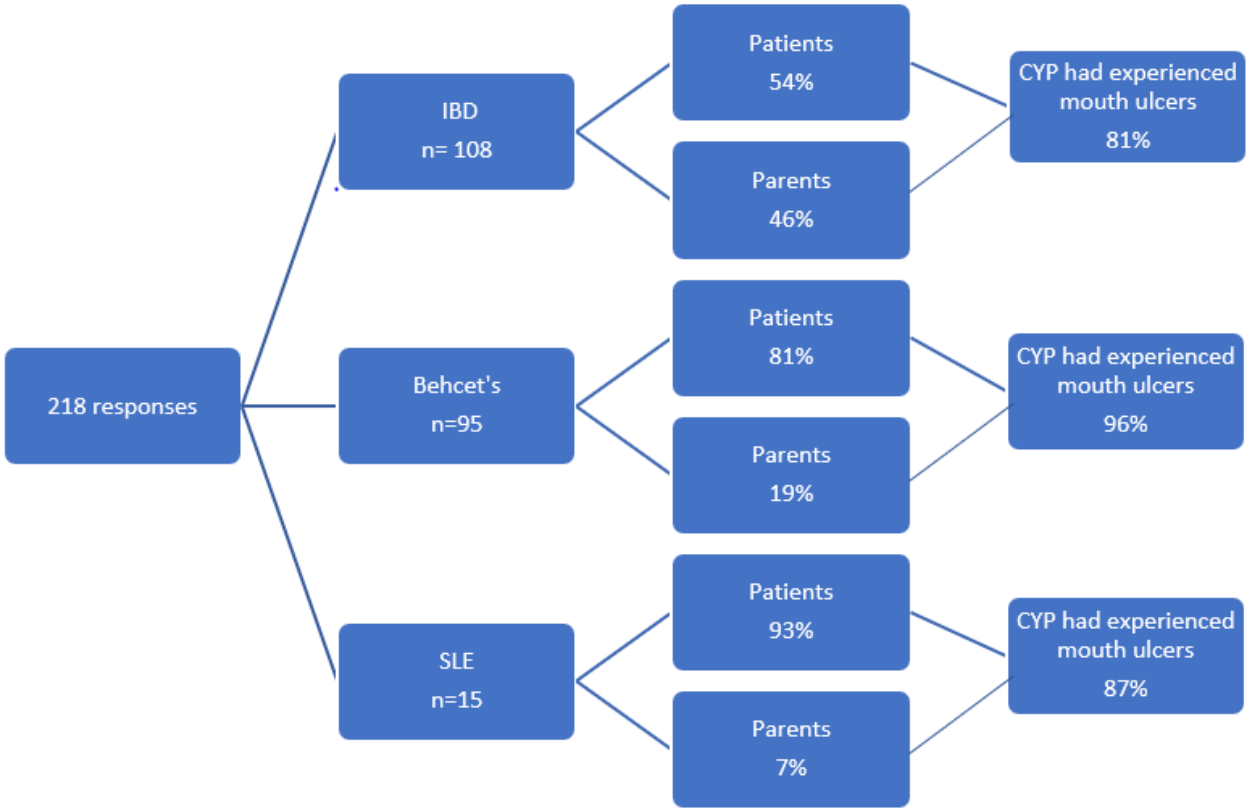

Figure 3-Flow diagram of characteristics of respondents to PPIE survey

3.3.2.1 Pre-diagnosis information

The information that patients/ their families would have found beneficial prior to diagnosis, for example when there was first mention of the condition, can be seen in *Figure 4*. This question was asked to see if an incidence rate ratio for systemic disease (as in the intended outcome for the CPRD cohort study) at this early stage would be considered beneficial, prior to prompting and in comparison with other information. The 'other' information suggested included: explanations of familial connection; other symptoms to expect (especially uncommon/ those not in criteria); age-appropriate explanations that did not assume knowledge; mental health and school support; dietary advise; and early investigations.

Respondents with experience of IBD and SLE would have found information relating to 'red flags' most beneficial prior to diagnosis, for example defining symptoms that should prompt attendance to A&E or further contact with the GP. In contrast, respondents with experience of Behcet's would have found practical information such as how to treat symptoms most beneficial, both pieces of information were

highly regarded by all groups. Other highly valued topics included an explanation as to why the symptoms had occurred, and a potential timeline to expect for example how long diagnosis might take, what appointments might look like following diagnosis or potential prognosis. The risk of a diagnosis was deemed beneficial in 7-12% of responses. This was within the two least popular responses in all groups, showing that most other information was considered more beneficial by patients/ their parents at this early stage in their diagnostic journey.

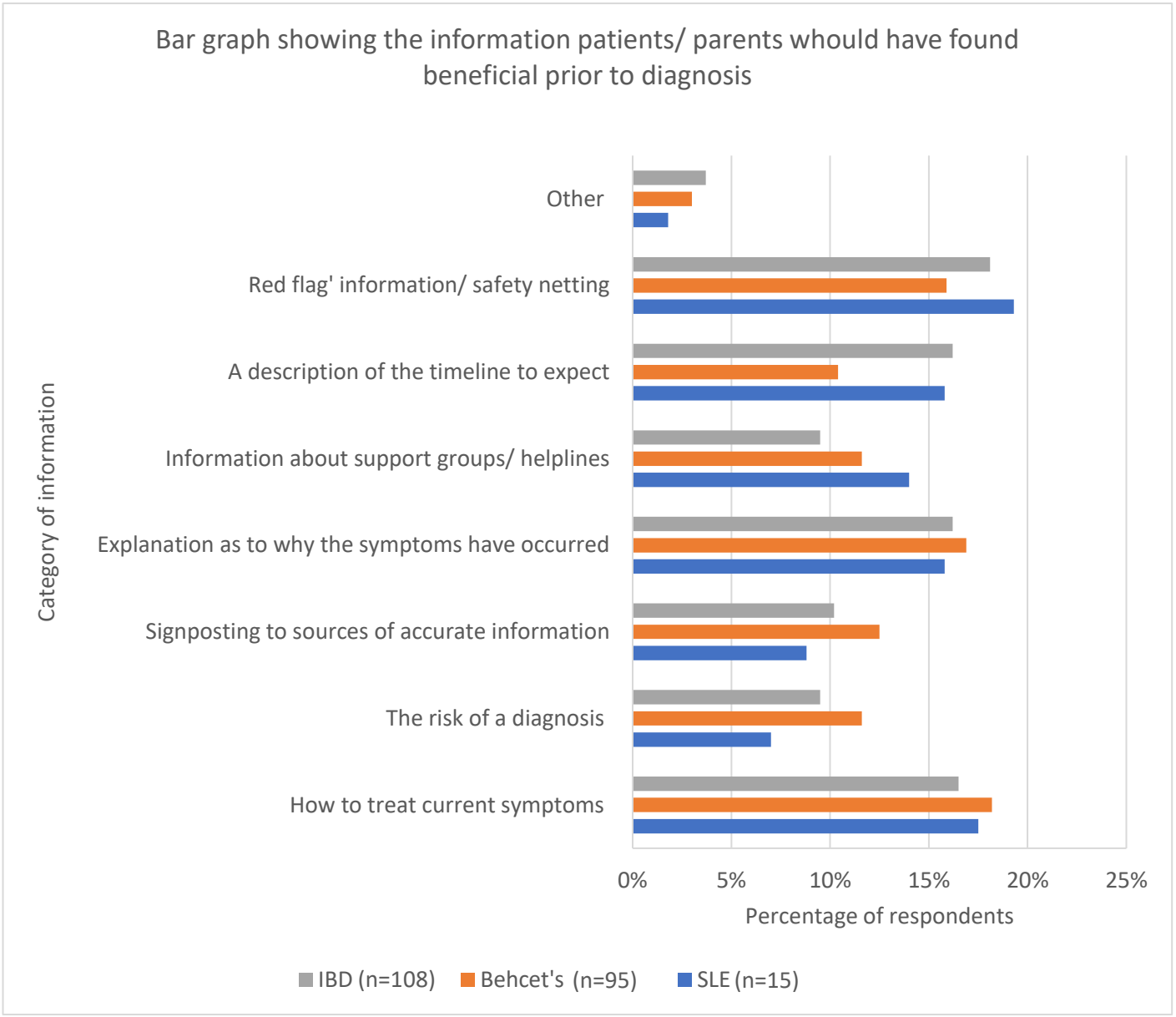

Figure 4- Bar graph detailing the responses of patients/parents to the question 'What information would have been helpful to you and your family at this stage?'. Stage earlier defined as pre-diagnosis.

3.3.2.2 CPRD Cohort study outcome

In terms of the main outcome of the proposed CPRD cohort study, calculating the risk of systemic disease in children who present to primary care with mouth ulcers, it was rated as 'somewhat good' or 'extremely good' by 40-57% of respondents compared to 'somewhat bad' or 'extremely bad' by 22-40% of respondents. Overall, the respondents with experience of IBD and Behcet's seemed to have a more positive reaction to the outcome, whereas the SLE respondents were more cautious. A full breakdown, by condition, of the rating of the outcome can be seen in *Table 11*.

Table 11- Responses of the patients/parents to the question 'Do you think that 'risk number' is a good or a bad outcome?'. Risk number previously defined to participants.

	IBD (n=108)	Behcet's (n=95)	SLE (n=15)
Extremely bad	3%	11%	20%
Somewhat bad	21%	11%	20%
Neither good nor bad	22%	20%	20%
Somewhat good	41%	32%	40%
Extremely good	13%	25%	0%

Respondent's explanation of positive ratings fell into six main categories: awareness, diagnosis time, preparation time, validation, reassurance and actions. These categories are elaborated upon below. However, they come with the caveat from many respondents that the IRR must be thoroughly proven and then fully understood by patients/ parents to be beneficial, as everyone's perception of risk varies. Some responses commented that the outcome was easy to understand so this is not perceived to be an issue in practice.

Awareness

Respondents felt that including this 'risk number' in common primary care practice would raise the profile/ awareness around their condition amongst primary care physicians (and in some suggestions dentists), particularly in the context of childhood-onset disease. It was felt that if the condition was in the forefront of a clinician's mind, they would be more likely to 'assess the bigger picture' and connect seemingly unrelated symptoms together, leading to an earlier diagnosis. One respondent suggested that increased awareness in primary care may have been 'life-saving' in their child's experience.

Furthermore, some respondents to the IBD survey hypothesised that increased awareness may lead to further research into the childhood-onset condition, which would be beneficial to patients and their families.

Time to diagnosis

It was felt that this increased awareness may decrease time to diagnosis, which was a key issue brought up by many respondents in all three conditions. If clinicians were considering the condition at an earlier stage this may lead to earlier testing, diagnosis and hence intervention which may reduce the rate of complications. It was also thought that if patients carried an 'at risk' label then future symptoms may be 'taken more seriously' by their GP which, again, could reduce their time to diagnosis. In line with this, parents felt that they would be better informed, if warned of a potential diagnosis, to monitor the symptom their child experienced to report to GPs or specialists and seek further investigations, hopefully further reducing time to diagnosis.

Preparation time

The extra time a warning of risk could be given that would give patients/ parents time to prepare for a diagnosis was seen as a major positive to the outcome. For example, many respondents felt that if they were able to understand the 'rare disease' prior to a diagnosis then this would decrease anxiety at the time of diagnosis, which could result in faster acceptance of their condition. Parents felt that they would be better equipped to support their child and possibly prepare or inform the school environment. It was also felt that there would be easier or faster access to support for both patients and their parents, following a diagnosis, because this information could have already been researched. One respondent summarised this category of feedback well: 'Knowledge is power'.

Validation

Many respondents described the validation a potential diagnosis would give them as a positive. It was suggested that mouth ulcers were not often taken seriously by clinicians and that the outcome of this research may tackle that, preventing the dismissal of 'just mouth ulcers' particularly in children. Honesty from clinicians was appreciated by respondents and they would like to know that all options for the cause of mouth ulcers were being explored, validating their concern, and potentially reducing the time children suffer for. It was expressed that 'a possible diagnosis was better than nothing', in that respondents would be relieved by some form of explanation as to why they/ their child had been experiencing symptoms. There would be a less uncertain future which could reduce anxiety because patients/ parents had at least some indication of what was to come. Overall, it seems that some empowerment would be felt by patients if their concerns for symptoms were to be validated by an IRR, particularly if delivered by a primary care physician.

Reassurance

The general consensus amongst respondents was that a low-risk figure may be reassuring, particularly if symptoms were mild.

Actions

Some respondents agreed with the outcome if there was a possibility to reduce the risk, for example to delay the diagnosis until adulthood, or reduce the complications that may occur. Evidently this would only be possible in some, if any, cases. This group of responses differed from the respondents that were keen to have more time to prepare for a diagnosis, as diagnosis was not seen as inevitable in this case which may be falsely reassuring.

The negative responses to the proposed outcome measure could be divided into five main themes: oversimplification, unnecessary worry, inappropriate, misdiagnosis and demoralising. The main points raised in each category are presented below.

Oversimplification

A lot of concern was raised around basing a risk calculation solely of the presence or absence of mouth ulcers, in that it is an oversimplification of the variety and complexity of presentation in these conditions. Many respondents commented on mouth ulcers being common and not necessarily indicative of the condition, stating that 'everyone is different' and the prediction could be 'inaccurate'. There were suggestions from respondents in all conditions that monitoring and consistent follow up may be a better approach. Some respondents with experience of Behcet's proposed a risk model based on extent, severity and frequency of mouth ulcers would be more acceptable. Whereas many respondents with experienced of IBD expressed their concern that mouth ulcers were not a common first symptom in their experience and that IBD should not be generalised in this context as mouth ulcers are more common in CD compared to UC.

Unnecessary worry

A key point brought up in many responses was the unnecessary worry that providing patients/parents with an IRR prior to a confirmed diagnosis may evoke, this was especially highlighted as a concern if the risk of diagnosis was low. Respondents raised issues such as 'health anxiety' and 'psychosomatic symptoms' that could be induced by the worry caused by proposing a CYP was 'at risk'. This was a key concern in the respondents with experience of IBD as they were aware that stress/ worry can exacerbate the condition. Some responses suggested that providing a potential diagnosis before it could be confirmed may lead to patients/parents accessing 'unhelpful research and scare stories'

which would increase their worry further. It was also commented that GPs were 'not best placed' to deliver this information because they do not have the expertise or access to support services, available in specialist care, to reassure or inform worried patients/ parents. Fear was a key concern amongst respondents as they were aware that a diagnosis itself is potentially scary, without worrying additionally about it beforehand. The general response was that this outcome would be 'too negative at an early stage'.

Inappropriate

Some respondents felt providing patients/parents with an IRR was inappropriate for the increased anxiety might cause. However, there were also concerns raised that children should not be involved if these conversations around risk were it to be had. At the less concerning end of the spectrum there was suggestion that an IRR would 'mean nothing to them', however there was greater concern that there would be a negative mental health impact on already vulnerable children, and that their aspirations could be affected if they viewed themselves as ill. An extension of this would be the point raised that being 'at risk' may affect employment prospects of young people and the wider issue of whether they would be protected under the Equality Act. Overall, the responses relating to this theme depicted an IRR as a burden, particularly to CYP.

Misdiagnosis

Potential misdiagnosis if an IRR was focussed on a singular diagnosis was a concern raised by some respondents, they felt an overall risk of autoimmune/ systemic diseases may be a preferable outcome. However, there was still concern that subsequent symptoms that could be attributed a different diagnosis/ condition may be dismissed by clinicians or patients/parents if an 'at risk' condition(s) had been pre-defined. Furthermore, some respondents expressed concern that providing a potential diagnosis before it was confirmed could lead to home remedies or dietary changes, particularly in IBD, without professional advise that could be harmful if the potential diagnosis was incorrect.

Demoralising

Some respondents felt that in providing an IRR, if a diagnosis could not be prevented or if treatment could not be offered until a diagnosis was made, this might be demoralising for both patients and their parents. The consensus in this group of responses was that practical help would be more beneficial prior to diagnosis, for example how to treat/ cope with the mouth ulcers. There was some expression that the risk of a diagnosis in the future was less preferable to a focus on the current circumstances.

3.3.2.3 Additional outcomes

The participants were then asked what other outcomes they would like to see from this or future studies, for example what information would patients/ parents have found helpful prior to a confirmed diagnosis. This prompt produced responses that could be divided into five main categories, which can be seen in *Table 12,* with examples.

3.3.2.4 Language

The final responses related to the language that would be most acceptable in this study. In terms of the phrase 'risk', a variety of options were given as alternatives, with 'chance' being the favoured word to replace risk in all respondent groups. The next most popular terms were 'likelihood' and 'probability'. 'Risk' itself most commonly ranked 4th in terms of preference and the only term it consistently was favoured over was 'susceptibility'.

The language used to describe the patients of the study was also put to a vote. 'Young people' was the favoured term in all respondent groups, and 'young adults' and 'teenagers' often followed in terms of preference. 'Children' and 'adolescents' were the least favoured terms. There were some additional comments that 'children' should still be included in the description of patients in the study as not to discount the experiences of people with early childhood-onset disease.

Table 12- Details of suggested additional outcomes, collected in phase two, categorised by theme

Category	Examples
Knowledge for patients/ parents (support)	• *Explanation of process to diagnosis* • *Specifically define other symptoms to monitor for, including common, uncommon and red flags symptoms (e.g. for flares and organ damage)* • *Sources of valid information, especially about treatment options* • *Reassurance that a 'normal life' can be led, for example positive experiences from other patients* • *Prognosis including best- and worst-case scenarios, life expectancy, potential complications, and typical timeline in childhood-onset disease (some respondents did not feel prognosis was appropriate prior to diagnosis)* • *Adjustments that can be made for example at school, dietary, lifestyle* • *Medications to expect and their typical side effects* • *Suitable transition services for young adults, particularly to ensure young people understand their condition before transition to adult care* • *Support groups* • *Mental health support*
Knowledge for others	• *Increased awareness/ education for clinicians on childhood-onset disease, especially in primary care:* - *Common symptoms including the typical links between symptoms* - *Consideration of the diagnosis sooner leading to faster referrals* - *Effective and compassionate communication to acknowledge/ validate patients and parents* - *More effective multi-disciplinary teams* - *(Specifically, in Behcet's and IBD it was felt that there should be more communication about genital ulcers and bowel symptoms to prevent embarrassment in young people)*

	• *Support for parents and siblings, including more effective communication*
Decrease diagnosis time	• *Decrease diagnosis time by linking common patterns of symptoms* • *Reduce the occurrence of misdiagnosis* • *Research into the damage of delayed diagnosis, to understand why it is important to avoid* • *Faster referral to specialists* • *Earlier testing*
Practical help	• *Faster treatment options for children* • *Suggestions for pain relief with mouth ulcers* • *Improved monitoring* • *Supportive, symptomatic treatment prior to diagnosis* • *Early dietician intervention, particularly in IBD* • *Social support, for example with eating in IBD, liaise with school, support mental health* • *Information on managing symptoms, for example medications for various levels of flare up* • *Clear treatment plans*
Future research	• *Causes of the conditions, both hereditary and non-hereditary* • *Better treatments with less side effects, and understand their mechanism better so they can be targeted to specific symptoms* • *Mental health impact of delayed diagnosis, especially relating to missed school and social activities* • *Occurrence of 'uncommon' symptoms* • *Risk calculations for diagnosis of other autoimmune diseases given the diagnosis of one* • *Indicators in early onset of the condition to aid early diagnosis* • *Plant based diets and their effect on mouth ulcers*

	• *Common misdiagnoses in each condition, in order to prevent them* • *Investigation as to why IBD causes mouth ulcers* • *Risk of surgery in disease course, particularly relevant to IBD* • *Is the age of diagnosis changing? Is there an increasing incidence of childhood onset disease?* • *Preventative measures* • *Predictors/ risk factors for the severity of disease course* • *Risk factors for/ links to other diseases*

3.3.3 Phase three: Final follow-up meeting with CYP

Six CYP attended the final meeting. They were all members of YourRheum and their ages ranged from 14 to 23 years. There were five females and one male present. The group will be referred to as CYP, despite their older age, for consistency also since they were sharing experiences from the entirety of their childhood.

The results of the CPRD cohort study were shared with the group in developmentally appropriate detail: CYP with severe mouth ulcers (severe enough to see their GP) are much more likely to be diagnosed with a systemic disease, but the individual risk of a diagnosis for a CYP with severe mouth ulcers is roughly 1% because the three systemic diseases (SLE, IBD and Behcet's) are rare.

Overall, the CYP felt that a 1% risk was low in the context of a diagnosis. They understood that 'most people would not go to the doctor with a mouth ulcer' so the risk of these conditions in the general population would be much lower than this 1%, even in the context of less severe mouth ulcers. A summary of all discussions in this final meeting are displayed in *Box 2 and* discussed below.

Box 2- Main findings from final meeting

Helpfulness

- *It would not be helpful to know the risk because 1% is a 'low risk'.*
- *Only helpful if the risk could be reduced.*

Emotions

- *Providing a risk percentage would cause a young person to feel scared or panicked.*
- *Being labelled as 'at risk' would increase health anxiety, as in the COVID-19 pandemic.*
- *Since the risk is small, it may be reassuring to some people.*

Communication

- *Positive language such as 'this percentage of CYP will not get a disease' is preferential as it helps to reduce anxiety.*
- *Patients should be informed of their risk in an age-appropriate way, and there are very few scenarios in which parents should not also be informed.*
- *Consultants should communicate risk in person, with a focus on directly explaining all information to the CYP.*
- *Reassurance and multiple sources of additional information should be provided during a conversation about risk.*

3.3.3.1 Helpfulness

The first topic of conversation was focussed on how helpful CYP thought it was to be provided with a risk percentage for a condition, before it could be officially diagnosed. The general consensus was that this information would not be helpful prior to diagnosis especially if the risk was 'only 1%' and would only cause worry. It was agreed that most of the CYP would have 'gone straight to google', if a risk percentage had been given to them in the context of their own diagnosis and worried themselves with a lot of information or potential misinformation. Overall, CYP felt that there would be increased stress on the patient and their parents prior to diagnosis which would likely be unnecessary since the diagnosis may not occur. They felt that even if the mouth ulcers did eventually lead to a diagnosis, providing a risk was still unnecessary since a confirmed diagnosis was very different from the uncertainty of a potential diagnosis: for example, CYP likened this scenario to mock exam results compared to official exam results.

With prompting, CYP formulated some scenarios in which providing a risk percentage may be helpful. For example, if the risk could be reduced or the onset of other symptoms could be delayed, however they acknowledged that this was an unlikely scenario. They likened the scenario to mock exams, stating that the risk of a potential diagnosis, prior to a confirmed diagnosis, was less helpful than mock exam results, prior to official exams, since the diagnosis cannot be changed, although preparation could be commenced in both situations. One of the attendees with Behcet's disease suggested that the provision of a risk percentage may be dependent on the severity of the symptoms and likelihood of the condition. For example, in the context of a potential Behcet's disease diagnosis in a CYP with recurrent, multiple, severe mouth ulcers and a positive family history; the risk in this scenario would logically be greater than 1% and a diagnosis of Behcet's disease diagnosis seems likely hence it may be acceptable to discuss this as a potential, in order to prepare the patient and their family.

Attendees that had experienced severe mouth ulcers suggested that treatment of their symptoms would have been more helpful than discussing potential diagnoses, and that redirection to other services such as pharmacists would have benefited them. It is interesting to note that this viewpoint came from CYP who were part of the '1%' of CYP with severe mouth ulcers that subsequently received a systemic disease diagnosis, as stipulated by YourRhem membership criteria (members must have a rheumatic condition).

3.3.3.2 Emotions

The group were asked how they would have felt if they were the patient with mouth ulcers that was told their risk of a systemic disease was 1%. Many of the attendees reported negative emotions such

as panic and feeling scared, especially if they were younger or had less experience of diagnoses or healthcare generally. Some stated that they would be confused if they had attended the GP with the expectation of treatment, since at that time they would not have associated mouth ulcers with 'anything serious'. There were comparisons drawn between being labelled 'at risk' during the COVID-19 pandemic, as many of these young people were, and being given a risk of a diagnosis. They agreed that this would increase health anxiety and cause them to be 'too aware' of the risk associated with their symptoms.

Many of the attendees reported neutral emotions to being informed of their risk of systemic disease, for example feelings of 'apathy' and being 'disassociated' or 'not bothered' were suggested in response however CYP acknowledged that their wealth of healthcare experience may have dampened their reactions in this type of scenario. Other attendees said that informing of the risk was 'random' or 'unnecessary' but it would not distress them, however it may have caused feeling of guilt, anxiety and disbelief in their parents.

In addition, there was some consensus that 1% was a 'small risk' and that this may be reassuring to some people. One attendee stated that it would be a 'relief' to have some explanation especially in the context of very severe symptoms, and that they think it is 'best to be aware' so they were not shocked later on.

3.3.3.3 Communication

Phrasing

The group were prompted to consider if they preferred positive or negative language when risk was being communicated to them. It was discussed whether risk should be stated as 'this percentage of CYP will get the disease' compared to 'this many CYP will not get the disease'.

Most preferred being told what percentage of CYP would not get a disease in the future, since they thought this would help them 'look at the positives' and reduce their anxiety by not focussing on the percentage of CYP that would get a disease. Some attendees preferred knowing the proportion of children that would get a disease because they 'don't like anything sugar-coated' and they would want to take the risk seriously, which they may not be prompted to if positive language was used. Overall, they felt that positive language was preferential for most patients. However, this could depend on their healthcare experience and the explanation that follows the risk statement.

Given the dyadic relationship between physicians and patients/ parents, it is important that there is never a generalised approach to consultation and physicians should always adapt to the needs of the patient/ family in front of them.

Who should be told the results?

As found in the 'helpfulness' section, most attendees did not consider it helpful to be told about their risk of a systemic disease. However, they felt that if they were to be informed then the acceptability of this would depend on the patient's maturity level, and that an age-appropriate explanation should be provided to all CYP as this will dictate how much they can comprehend. Again, the severity of the patient's symptoms and hence the likelihood of a potential diagnosis should inform a clinician in their discussions about risk. Unsurprisingly in this group of CYP with a wealth of healthcare experience, they highlighted that a patient's experiences may affect (either positively or negatively) their ability to cope with a conversation about risk of a diagnosis.

Most attendees felt that parents should always be told if the risk to their child was high, however some felt that confidentiality was important if the patient was a mature and independent young person. Their definition of this ranged from aged 14 up to 18 years, dependent on the individual situation. It was agreed that parents should be able to decide how and when a CYP is told about their risk if they are less than 10 years old, as no attendee deemed themselves mature enough to comprehend risk at this age. One attendee stated that they felt 'invincible when (they were) younger'. Overall, the consensus was that if parents were to be told about risk, given the parameters discussed, then they should be given more information than the patient as they have a greater capacity to deal with the information.

Who should communicate the results?

All attendees felt that their consultants would be best placed to have a conversation with them and their families about risk. A key point they wanted to raise, following the COVID-19 pandemic, was that these types of conversations needed to happen in person and that a letter would not be acceptable. It was discussed that if the conversation had to be done in primary care, then a referral should be made to specialists immediately following this.

It was highlighted that some CYP felt 'kept in the dark' during their journey to diagnosis, especially as children. They felt it was the responsibility of doctors as well as parents to ensure this did not happen,

and an important step towards this would be directly informing the CYP about risk once they were mature enough.

Additional information

All attendees felt that if risk was to be communicated, reassurance was also necessary given the increased anxiety this may cause. There was disagreement as to whether more information was required prior to a confirmed diagnosis, however many attendees felt that during their own diagnostic journey they did not receive enough information. Some were keen to highlight that 'too much information' could also be detrimental and that necessary information may get lost.

In terms of the sorts of information sources that YP found useful, there were many suggestions: 'trustworthy websites' as alternatives to google; videos; leaflets giving 'simple' information; and the 'Health-unlocked' website because it allows YP to 'speak to someone directly'. Overall, there was an agreement that information should be provided in a variety of forms since each CYP has an individual preference. It was also suggested that this would allow information to be passed on to a CYP's school, particularly PE teachers, to allow better understanding and adjustments to be made outside of a healthcare setting.

3.4 Discussion

Overall, the findings of this PPIE input gave a mixed picture as to whether the results of the CPRD cohort study would be best communicated directly to parents and patients, highlighting that care should be taken when applying results of the study to clinical practice. However, in all stages of PPIE input there were points raised that supported the proposed primary outcome of the CPRD cohort study. Some consensus was reached, across the first two phases of PPIE activity, as to what language should be used in the delivery of the cohort study findings, however there will always be discrepancies due to personal preference and lived experience.

3.4.1 Sequential information

Each phase of this investigation was able to inform the next sequentially, as well as providing their own insight individually. The first phase was able to gauge initial opinion on providing patients/ parents with an IRR to constitute risk of systemic disease in CYP presenting with mouth ulcers to primary care. It particularly highlighted that this outcome would not be acceptable unless provided

alongside actionable information, for example support groups or earlier intervention. This informed the question regarding helpful information prior to diagnosis, which was included in the survey phase, which allowed the statements made in the first phase to be quantified with a greater number of responses. Also, it allowed the comparison of the proposed outcome to potential resources that are currently available.

Furthermore, the language discussions in the initial meeting provided terms to include in the surveys in order determine wider opinion. It also narrowed down the number of terms to be assessed, for example 'mouth ulcers' and 'systemic disease' were not consulted on in the second phase as there was a consensus in the first meeting that these were acceptable and easily understood with simple explanation.

The first two study phases informed the language to be used in the presentation of study results during the final phase. This enabled more effective and acceptable communication with the attendees. The three themes in the final meeting were informed by opinions collated by the previous two stages. Helpfulness was assessed to gauge whether the outcome would be acceptable individually, given the inclusion of the accurate study calculations, or if additional information was required as highlighted by the initial phases. Emotions relating to the outcome were assessed to determine a true reaction from participants with lived experiences given verified information, in order to discover which of the theoretical positive/ negative responses to the outcome, from the previous phases, stood true. Finally, the communication theme was included as a direct response to comments in the survey suggesting that 'GPs are not best placed' to give the information to patients, and that the outcome was 'too much' for children to receive.

3.4.2 Positive feedback

A common theme across the first two phases of the study was that an IRR may be reassuring to patients/ parents. However, in the first phase this feeling of reassurance was believed to come from being informed and empowered about the risk so that symptoms could be monitored. Whereas in the second phase it was suggested that reassurance would only come from the risk being low. However, in the second phase monitoring symptoms it was also commented on in terms of reducing time to diagnosis. In the third phase it was agreed that the 1% risk was low and hence may be reassuring to some people however none of the young people in attendance felt this personally.

In the second phase, themes also arose that were not suggested in the first phase for example preparation time, raising awareness and validation, which understandably came from the perspective

of experiencing a rare/ childhood-onset disease diagnosis. As diagnosis was not a requirement for participants in the first phase, this could explain the narrower perspective of this group. However, none of these themes arose in the third phase involving solely CYP so it could be hypothesised that this was a parental perspective from the second phase.

Groups in all phase groups highlighted that the outcome would be the most beneficial if the risk of systemic disease could be reduced, or at least the risk of potential complications could be diminished. Further research would be required to assess if earlier intervention, given risk calculations, could affect the subsequent disease course in any of the three conditions.

3.4.3 Negative feedback

Both initial phases acknowledged that providing an IRR to children may be overwhelming. However, the first phase participants suggested limiting information given to children, striking a balance between realistic and scary, however respondents in the second phase deemed any information about risk 'too much for a child'. In the third phase it was agreed that younger children may be confused by the concept of risk, however from the personal experiences of these young people they felt keeping children 'in the dark' during diagnosis was not acceptable, which echoes the view of young people in the first phase. This difference in opinion could be due to the fact that parents were included in the second phase and naturally they want to protect their children, particularly in the case of children with health issues. However, the responses from the young people in the first and third phase suggests that CYP are capable of handling more information than a parent might expect and that they are keen to be involved in their own care.

'Unnecessary worry' was a phrase that appeared in both the first and second phase of investigation, and also reciprocated in the opinion in third phase participants who deemed information about risk unhelpful due to increased health anxiety. First phase participants suggested that having nothing actionable alongside the IRR would be anxiety inducing, however second phase respondents were more concerned and suggested that the worry caused by stating the risk would always be unnecessary even in the presence of additional information. Participants from the third phase, acknowledged that despite the risk being 'low', the mention of a diagnosis would still cause worry if it could not be confirmed. Practical help was highlighted as important by participants in the first two phases, for example symptomatic treatments and support groups, otherwise patients/ parents may feel demoralised. Whereas in the third phase, young people were keen to be given multiple forms of information. This discrepancy may have arisen from the phrasing of this question in the final meeting.

Again, the second phase respondents raised points that may have come with experience of the conditions such as: calculating risk merely from the presence of mouth ulcers is an oversimplification of the issue; and the risk of misdiagnosis would be increased if this calculation was made at an early stage. Third phase participants, also with experience of long-term health conditions, did not voice these concerns however they did express that it was 'random' to be given a risk percentage if they had attended a GP with mouth ulcers, which may allude to the 'oversimplification' point raised by the second phase respondents.

3.4.4 Language

There were some discrepancies in acceptable language preferences between the first and second phase respondents. The first phase participants expressed a consensus preference for the term 'risk' in this context as they felt it conveyed the correct level of seriousness, whereas 'chance' was determined to be too 'watered down' given the potential severity of the situation. In contrast, 'chance' was the most preferable term amongst the second phase respondents and 'risk' was poorly ranked. Parental perspective in the second phase may have skewed the results as it would be understandable that parents may want to use more 'watered down' terms when discussing their children's health. However, it could also have been that the first phase participants did not understand the emotional/ negative connotations of the more severe term since they did not have lived experiences of the three conditions. Finally, the number of respondents could give an explanation: 15 participants in the first phase was liable to be skewed by personal preference of the small response pool, however the votes of 208 respondents in phase two may be a more reliable depiction of the general opinion of the population.

'Young people' was the preferred term to refer to patients in the study, across both groups. However, some comments stressed the inclusion of 'children' in this term to validate the experiences of patients who get a diagnosis at a young age, and their parents.

3.4.5 Informing the CPRD cohort study

The comments on language from each phase, as discussed above, were collated to inform how the cohort study was designed and presented. For example, the term 'children and young people' was used to describe patients based on feedback from the two initial phases. 'Systemic diseases' remained as the umbrella term to define SLE, IBD and Behcet's, although a description of the term was added, following comments from the phase one respondents. 'Risk' remained as the term used in the thesis

write up as it more clearly defined IRR however when results were communicated to patients/parents, for example in leaflets or meetings, the term 'chance' was be used as deemed preferential by respondents in the second phase

The concerns raised around the outcome measure of the study were included in the discussion about the application of the results to ensure patients/ parents were considered when communicating results.

3.4.6 How the results of the CPRD cohort should be used

The findings in phase three of this PPIE involvement suggest that young people would not wish for the risk calculations of the CPRD cohort study to be incorporated into primary care practice. It is understandable that young people who already have a diagnosis and have to deal with all of the challenges that come along with that, would not be interested in being informed of a 'small' risk. It would be interesting in future work to hear the views of young people without long term health conditions on the final results of the CPRD cohort study.

Phase two findings suggest that respondents would like to see GPs informed of the risk to raise awareness of the three conditions to aid faster diagnosis. Further surveys could revisit the views of participants in the second phase to discover if their opinions would remain given the numerical risk findings of the cohort study.

All phases combined highlight that young people and their parents have a desire to be involved in conversations about risk and its research, and hence a summary of the findings of this PPIE study should be included alongside the presentation of risk calculations in the CPRD cohort study.

3.4.7 Limitations

There were some limitations to the PPIE activities carried out which included access, ensuring appropriate representation, and risk of bias.

The first two phases of activities required internet access which may have excluded participants without internet connectivity, hence underrepresenting this group. Furthermore, all phases of activity were conducted in English which may have restricted the participation of people who do not speak English as their first language. An underrepresentation of non-English speakers may have led to an underrepresentation of certain ethnic groups. No data was collected on ethnic background and hence it cannot be confirmed if the participating group was representative.

In both meeting phases, participants were required to be a member of a young person's advisory group (either GenR Liverpool or YourRheum). Hence there is a risk that the views expressed by these participants are not reflective of the general population, since members of the groups have a keen interest in informing research. Furthermore, members of GenR are not required to have a medical condition and hence the results of the first phase may not be representative of the opinions of CYP with a systemic disease. Also in both meetings, there was a risk of consensus bias or 'groupthink', in which it is known groups have a tendency toward concurrence (159), hence views of quieter members of the group or those with opposing opinion to the general consensus may have been underrepresented. The bias caused by 'groupthink' was reduced by the presence of an experienced facilitator who attempted to initiated conversation around all participants' views and redirected efforts to reach consensus. The activities were also consciously designed to avoid 'groupthink': all attendees were encouraged and given opportunity to formulate ideas prior to group discussion and voice their opinion in conversation.

In the survey phase, participants were recruited via charities associated with each systemic disease (Lupus UK, Crohn's and Colitis UK, and Behcet's UK) and participation criteria specified that either themselves or their child must have been diagnosed with either SLE, IBD or Behcet's. Thus, the views of people that had experienced mouth ulcers in childhood that did not result in a systemic disease diagnosis were not represented in the survey responses. It could be hypothesised that a population lacking experience of systemic disease may have concurred more with the 'unnecessary worry' and 'inappropriate' themes, which were suggested by the population with experience of systemic disease, in their views of the proposed outcome of the CPRD cohort study.

3.4.8 Future research

In phase two, many additional outcomes were suggested by respondents. However, the most applicable to the cohort study were: risk calculations for diagnosis of other autoimmune diseases given the diagnosis of one; investigation as to why IBD causes mouth ulcers; incidence of childhood-onset disease; preventative/ delay measures for onset; predictors for the severity of disease course. Clearly there is scope and desire for further research into the issue of childhood-onset systemic diseases, and it is important to collate the opinions of patients and their families to ensure future study outcomes are applicable to their needs.

Initially, it was anticipated that an additional proposed case-control study of CPRD data would also take place. However, the significant challenges relating to the other components making up this thesis, and especially the CPRD cohort study itself, precluded this being able to be done. However, a CPRD-

based case-control study would be able to answer some interesting research points raised by respondents such as: typical patterns of symptoms at presentation; occurrence of 'uncommon' symptoms; and diagnostic indicators at early onset. The case-control study has the potential to assess the full presentation profiles of patients with childhood-onset systemic disease and hence the contribution of other symptoms in addition to mouth ulcers in terms of risk, can be assessed. This was a key concern amongst phase two respondents who expressed that assessing other symptoms would prevent oversimplification of the issue as in the cohort study outcome. Both CPRD study designs combined (cohort and case-control) intended to assess the issue in its wider context and hence satisfy some concerns and additional outcomes raised by patients and their parents.

3.5 Conclusion

A three-phase approach to PPIE input has sequentially informed the collation of patient and parent views, as well as collectively informing the outcomes and presentation of the cohort study. Both positive and negative feedback on the proposed outcomes were considered when designing and presenting the results of the cohort study. Language used in the cohort study has been informed by feedback from patients and their parents to confirm acceptability. Overall, the PPIE input the cohort study received has been invaluable in ensuring relevance to the population the results intend to benefit.

4 Chapter 4: CPRD Cohort Study

Assessing the risk of systemic diseases, such as Behcet's, SLE and IBD, in CYP that have a code for mouth ulcers in their primary care record: A descriptive, observational, cohort study using the Clinical Practice Research Datalink

4.1 Introduction

Clinicians and healthcare professionals have made the association for very many years that some CYP initially presenting with mouth ulcers (usually recurrent) may later go on to develop a systemic disease such as SLE, Behcet's disease or IBD. However, it is also known that the majority of CYP with mouth ulcers will not go on to develop such a serious diagnosis, since systemic disease is very rare compared to the commonality of mouth ulcers. In the general population of CYP, mouth ulcers are significantly more common than systemic disease diagnoses, as discussed in *Section 1.1*. Mouth ulcers do not always appear as a symptom prior to the diagnosis of systemic disease, particularly in SLE and IBD. This has been illustrated by the systematic review above (see *Section 2*). Mouth ulcer frequency at onset ranged from 55-98% (71-74, 76-79, 81-85, 87, 89, 91) in Behcet's compared to 3-74% (17-33, 35, 36, 38-47, 49, 52, 53) in SLE and 0-44% (93, 94, 96, 98, 99, 102, 105, 107-109) in IBD. Clearly not all CYP with mouth ulcers will subsequently be diagnosed with a systemic disease and not all CYP with a systemic disease began their diagnostic journey with mouth ulcers. However, clinically, it is important to understand the risk of progression from mouth ulcers to systemic disease as this is a potential treatment opportunity timeframe or at least an opportunity for suitable preparations to be made prior to a serious diagnosis.

The systematic review above (see *Chapter 2*) has highlighted gaps in the current literature that a cohort study specifically looking at the issue of systemic disease risk in CYP with mouth ulcers will contribute to filling. The review highlighted not only that this risk has not been quantified by any published literature to date, but also that the risk may be affected by age, sex, ethnicity and/or other factors. Hence, the potential risk of development of systemic disease following mouth ulcers should be stratified by these factors in this cohort study.

The present study reviewed primary care data specifically, since this was an area not covered by any current published literature (which presented mainly hospital settings). This current study sought to capture the patient journey from their first presentation with mouth ulcers to health professionals, which typically takes place in primary care.

Primary care records were extracted on a cohort of CYP aged under 16 years (at first mouth ulcer presentation) from the Clinical Practice Research Datalink (CPRD) database (160). The CPRD database is a resource providing access to anonymised UK primary care records and other linked databases for the purposes of clinical and public health research. The resource has been active for more than 30 years and holds data on >60 million patient records from approximately 2,000 contributing practices (160). Incidence and rate ratios were calculated to determine the risk associated with mouth ulcers in relation to systemic disease. Multifactorial analyses were used to determine if these risks were associated with other factors such as sex, age, ethnicity and index of deprivation, as informed by the systematic review.

4.2 Methodology

4.2.1 Protocol submission

To receive access to CPRD data, a protocol application (*Appendix C*) had to be made to the CPRD via their online portal. The application included: general information about the proposed research study; details on the type of data that needed to be accessed including linked data; and protocol information summarising the study background, aims/ rationale, design, feasibility, population/ controls, outcomes and analysis. The study protocol outlined a detailed approach to addressing confounding and missing data, involvement of patient groups, and dissemination plans of the study's results. Limitations of the study had to be identified and acknowledged to complete the application. Following submission and some minor amendments, the protocol was approved and access to the CPRD data was granted. A separate request for linked data had to be completed on the online portal in order to receive index of multiple deprivation (IMD) data from a linked database to the CPRD.

4.2.2 Ethics

Ethical approval was not required for this study, in line with other CPRD-based studies, since it was secondary analysis of data that had been anonymised by an external party and was provided to the research team in a fully anonymised format, as confirmed by the research ethics team at The University of Liverpool (UoL). The CPRD has ethics approval from the Health Research Authority (161). Once they receive data from research active practices they ensure it is fully compliant with the Information Commissioner's Office (ICO) anonymisation code of practice and that patient privacy is protected(161). Hence following protocol approval via the CPRD Research Data Governance (RDG) process, the data extracted can be used for public health research by bona fide researchers (161).

However, throughout the study researchers are governed by robust terms and conditions on how the anonymised data is used (161).

4.2.3 Study population

The study period was from 1st January 1990 to 31st December 2019. There was a variety of reasons for these limits. The earlier limit was because CPRD data is most accurate from approximately 1995 onwards due to more accurate record keeping (160). However, a long follow up time was required hence 1990 was deemed appropriate. The upper limit was to avoid the data being affected by the COVID-19 pandemic that occurred in the UK from March 2020. The timeframe length was deemed to be include a long enough follow up period to provide meaningful outcomes. The study had an open design with patients entering when they were registered at a research active practice and met the inclusion criteria for the study. Patients exited the study at their transfer out date, death date, practices' last collection date or 31st December 2019, whichever was earliest.

In this cohort study, the exposed group were CYP with mouth ulcers recorded by their general practitioner (GP). A record of mouth ulcers was defined as at least one Read code for mouth ulcers in the CPRD record, specified by the formulated code lists for all possible mouth ulcer diagnoses, *see Appendix D*. Read codes are a clinical terminology system used in UK primary care to allow comprehensive clinical encoding of demographic and healthcare information. The index date for exposed participants was the date at the first record of mouth ulcers.

The comparison group of CYP did not have a prior record of mouth ulcers and were frequency matched to exposed participants at index date by age (+/- three months) and sex at a maximum ratio of three to one. If any participant had a record of the defined outcomes (below) prior to their index date, they were excluded. The index date for matched participants was the pseudo-index date for unexposed participants. The full inclusion/ exclusion criteria for all participants are shown in *Table 13.*

Table 13- Inclusion/ exclusion criteria for participants in the cohort study

	Inclusion	Exclusion
All participants	• Data meeting CPRD quality standards • Permanently registered CYP aged ≤16yrs • Patients for whom Patient Level IMD is available • Patient records have an acceptable patient flag	≥ 1 code for any outcome prior to index date/ pseudo-index date
Exposed participants	≥ 1 code for mouth ulcers in CPRD record	• No matched participants available • Mouth ulcer code related to infection or neoplasm
Unexposed/ comparison participants		• ≥ 1 code for mouth ulcers in CPRD record • Sought no medical attention after pseudo-index date

4.2.4 Outcomes and covariates

There were three main outcomes for this cohort study: a diagnosis of Behcet's disease, IBD (Crohn's, ulcerative colitis or non-specific IBD) and SLE. The outcome code had to occur after the index date but could be at any age, and were defined by Read code lists, see *Appendix E, F and G.*

All code lists for this study were formulated by the primary author (NG) prior to protocol submission. This process involved searching for diagnosis terms in the 'Code Browser' application and then using the codes assigned to these terms to collect other relevant terms. The process was repeated until we were satisfied that all possible codes that could define the diagnosis were collected, to ensure the lists were not unduly biased towards commonly used terms/codes. The completed code lists were reviewed by the supervisory team to ensure clinical relevance.

Multiple covariates were considered when analysing the results of this cohort study, informed by the findings of the systematic review. These are listed in *Table 14* alongside their definitions.

Table 14- Definition of covariates

Covariate	Definition
Age	At index date
Sex	Defined using the CPRD sex variable
Ethnicity	Defined using CPRD
Socio-economic status	Evaluated by assessing patient-level IMD scores and categorising into decile of deprivation (1st decile= most deprived, 10th decile=least deprived)

4.2.5 Data extraction

The code lists for mouth ulcers and outcomes was supplied to a designated CPRD fob holder within the University of Liverpool. They were then able to create a patient ID list of exposed patients and a separate list of matched, unexposed patients. From these lists, all patient records could be extracted from the CPRD database. These records included, for example: observation, consultation, drug issue, problem, referral, staff and practice files, *Figure 5* details the data included in each of these files and how they are linked. Linked IMD data was also extracted from the database using patient ID lists.

The extracted data was downloaded and made available via a research data drive on the UoL network. Each type of data (e.g. consultation files, observation files etc.) was contained in an individual text file which were grouped into folders based on whether the patient was categorised as exposed or unexposed. The IMD data was also shared in this way.

4.2.6 Data analysis

Data analysis was carried out using and in the R software (162) as this this is considered to have the strongest capabilities to manage large datasets. It is also an open-source, free software, hence there is more opportunity for shared code scripts and packages online, which would benefit a new R user. Familiarisation with the software took place through an 'R for Beginners' course ran by the Computational Biology Facility (CBF) at the UoL. The three-day course covered the basics of R language, base graphics, visualisations with ggplot2 and an introduction to statistical analyses in R.

The files were downloaded onto the UoL supplied laptop to prepare for reading the files into the R software. The observation files were filtered using the mouth ulcer code list to only include the first

occurrence of mouth ulcers in a patient's record. This was then combined (using patient ID number) with the demographic files, hence creating a data table from which summary statistics for the exposed population could be deduced.

A script was run on the combined demographic and observation data table to find the distribution of sex, IMD decile, age at first mouth ulcer code and year of first mouth ulcer code (summary statistics). A further script, using the systemic disease code lists, was run on all of the observation files of the included, exposed population to filter for the first code for a systemic disease. These patients were then filtered again to ensure the first systematic disease code occur after the first mouth ulcer code. A similar summary statistic script was run on the exposed population, who also had an outcome, to determine the distribution of the three conditions, age at onset and time to diagnosis. Following this step, a table of summary statistics was created for the exposed population.

The unexposed population supplied by the initial data extraction was filtered, to represent the exposed population that had been filtered extensively by age, mouth ulcer code, date and availability of IMD data (explanation in *Section 4.2.6.1*). The aim was to have a sample of patients without mouth ulcers that were similar in index age and sex to the extracted population with mouth ulcers at a maximum ratio of 3:1. Individual matching was deemed unnecessary to enable assessment of the contribution of age and sex distribution to the risk of systemic disease in CYP with mouth ulcers. In theory all CYP without mouth ulcers could be analysed as a comparison population. However, the CPRD does not permit the use of the whole CPRD dataset. A sampling frame for unexposed patients was created from the number of each sex with each year of birth in the unexposed population (for example if there were 20 males born in 1999 in the population with mouth ulcers, there needed to be a maximum of 60 males born in 1999 in the unexposed population). This frame was used to extract unexposed patients from the pool of patients that had originally been extracted from the CPRD database to be used as a comparison group.

Both exposed and unexposed patients were grouped by year of birth and sex (for example all males born in 2004 etc.) and the median first mouth ulcer code date (index date) of each exposed group was assigned as the pseudo-index date to all members of the corresponding unexposed group. Once a comparison cohort had been created, the summary statistic code script was run on the unexposed population dataset and a table of the results was created. This sampling frame method was determined more accurate than a random sampling method since it created a broadly similar unexposed group in order to assess the potential confounding of age and sex.

The outcomes were examined in each arm of the cohort separately (exposed and unexposed). An outcome code had to have been coded for at a date later than that of the index/pseudo-index date to

be included. The summary statistic script was run again on each group and tables of the results were created. The 'outcome' groups were further divided into the three systemic diseases of interest (SLE, IBD and Behcet's) and the summary statistic process was repeated.

Incidence rates for all and each of the outcomes in the exposed and unexposed populations were calculated using the following calculation:

Number of participants with an outcome/ Total time contributed by all participants in group

Time contributed was determined by the interval between index/pseudo-index date and end date. End dates are defined in *Section 4.2.3*. Following this calculation, incidence ratio ratios were formulated for all and each of the outcomes by comparing the incidence rates in the exposed and unexposed populations.

After initial incidence rate calculations, incidence rate ratios (IRRs) were modelled using a Poisson regression model. The model was applied to the cohort in its entirety, with the primary exposure of presence / absence of a mouth ulcer code and additional adjustments for, index age, sex and IMD group. Following this the cohort was stratified by outcome: each of the individual systemic diseases (SLE, IBD and Behcet's) as the sole outcome. Again, the models were adjusted for age and sex, the IMD was added as an adjustment. The cohort was then re-stratified into various sub-populations of age, sex and IMD level, with systemic diseases collectively as the outcome in the models. Each model was adjusted for the two variables it was not stratified, for example the stratified age group models were adjusted for sex and IMD level.

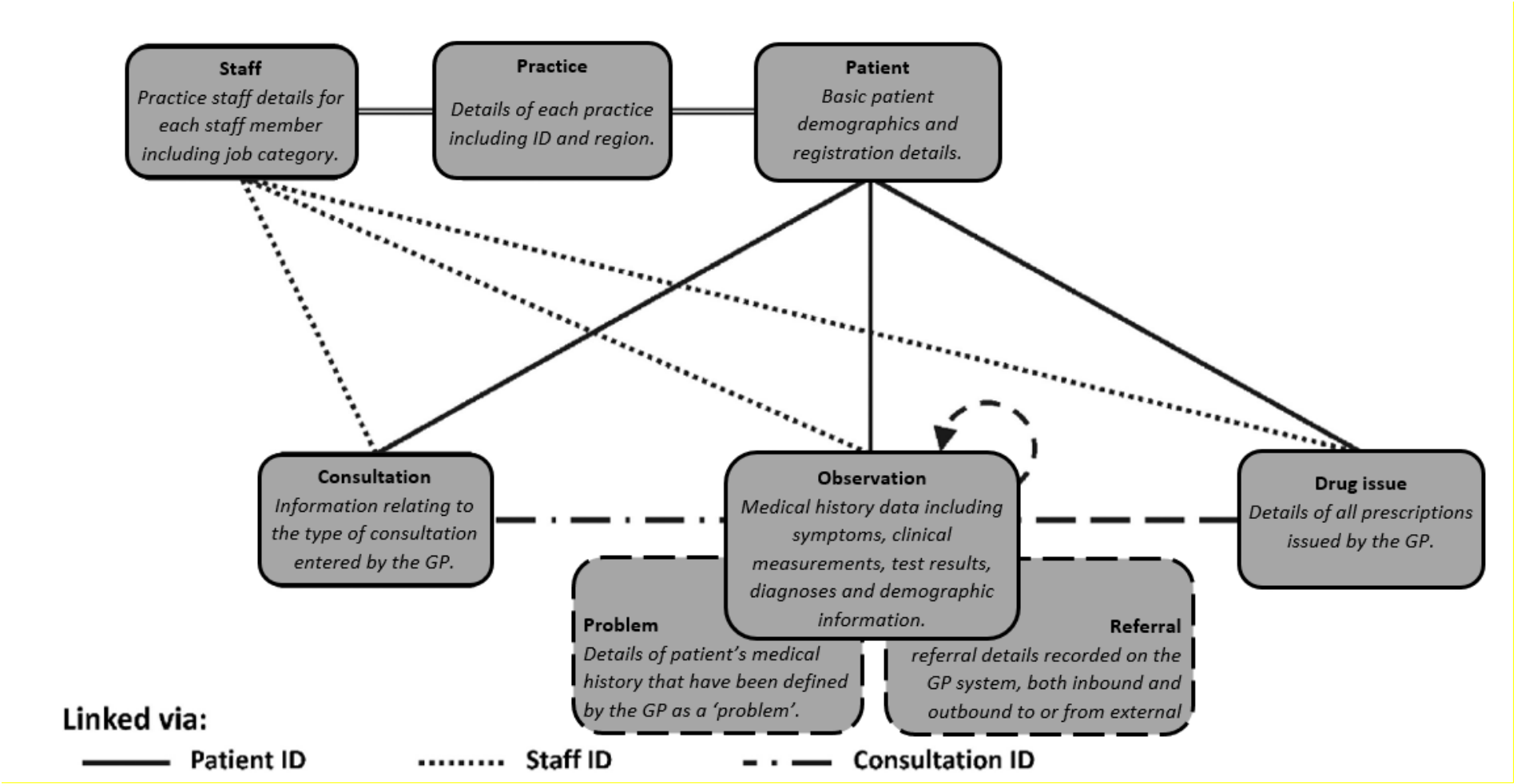

Figure 5- Schema of CPRD Aurum data files and their linkage- Adapted from Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum (160)

4.2.6.1 Challenges in data analysis

Following the R course, initial efforts were made in tackling the analysis of the dataset. However, a number of issues subsequently arose at all stages of data analyses which prolonged the process, some key examples of which are summarised here. The initial intention was to read all of the exposed patient files into the R software and create a large data table containing all of the required information for the analysis. However, with over 350k patients identified with multiple files in each category of file, the data table was too large for the storage capacities of the software. Preliminary attempts were made to resolve this problem, following extensive online research, by increasing the storage capacity of the software. For example, using codes to increase the storage capacity the software allows a data table to use, and trying different methods to read in the files so they used less storage individually. Unfortunately, these attempts were to no avail and the data table was still too large.

An underlying problem with reading the files in was identified whilst attempts were made to resolve storage issues. As the files were stored on a research data drive on the UoL network, the system had to be connected to a VPN which required internet connectivity. Whenever there were even momentary lapses in connectivity the reading process would cease as the files effectively did not exist in the system. Each time this happened, the process would need to be manually restarted, usually resetting code that had been running for hours. Also, because the system was downloading the files from the network whilst reading them into the R software the code took longer than it should have to run, even when connection was suitable. After attempting to use a more stable network connection on campus and consultation with team members from the CBF, it was advised that the files should be downloaded onto a UoL supplied laptop before running the reading in codes. This solution solved both the speed and connectivity issues, allowing the files to be read in more efficiently. However, the storage capacity trouble remained.

Many contacts were made with regards to the storage capacity problem including to the CBF team members, colleagues working on CPRD projects at the UoL and fellow students. Eventually it was deemed that every avenue had been exhausted to create the data table that was initially planned, and a different approach would be required. A CPRD colleague shared an R script that had been used previously to filter files and on closer inspection of this it was thought that a data table containing all of the files may not be necessary.

Once files had been read in, it became apparent that some patients had been included in the original, supplied dataset that did not meet the inclusion criteria of the study. For example, some patients were older than 16 years at their first mouth ulcer code, their code they had for mouth ulcers had an infectious cause, or their first mouth ulcer code date lay outside of the study dates. The original

dataset had to be filtered by date, age at first mouth ulcer code and by non-infectious mouth ulcer codes to formulate a dataset containing only patients that met the inclusion criteria. The summary statistic script was then run again on the true dataset to find summary statistics.

The IMD data was not available during the first stages of analysis, the steps to create summary statistics for both the exposed population as a whole and those with an outcome code had to be repeated. This was due to the fact that some of the original exposed population did not have IMD data available (despite IMD data linkage being a condition in the data extraction process), hence they did not meet the inclusion criteria for this study.

Once the exposed population data had been filtered extensively, the extracted unexposed population was no longer sufficiently similar to be used in comparison. The supplied, unexposed population had to be filtered by age and sex so that it was comparable to the exposed population. However, this proved difficult as age could not be determined without comparing the date of birth and pseudo index date of an unexposed case, but the pseudo-index date could only be found by individually matching to an exposed case and using their 'date of first mouth ulcer code'. Support was again sought from various sources. However, this was a very specific coding issue to frequency matched cohort studies, which meant that informed advice was lacking. Eventually the solution was found in an R script that had previously been used by a colleague for a similar issue. Age was substituted for date of birth for use in this script, as this data was available prior to matching.

Issues in data analysis were exacerbated by the departure of one supervisor from UoL which led to reduced CPRD and public health research knowledge in the supervisory team. Thus, support had to be sought from other sources which proved more troublesome than initially anticipated.

4.2.7 Case control study

In the protocol submitted to the CPRD there was also an application for access to data for a case-control study that would further assess the risk of systemic disease in CYP that present to primary care with mouth ulcers. As the outcomes of interest are rare within paediatric populations, a case-control study would give a broader picture of how CYP with a systemic disease diagnosis initially present, with a focus on mouth ulcers. The plan was to examine the odds of prior coding for mouth ulcers in a population of CYP with a diagnosis of SLE, Behcet's or IBD (cases) compared with an age and sex-matched cohort of children without systemic disease.

As described above (*Section 4.2.6.1*), there were significant methodological challenges faced in data analysis for the cohort study itself that resulted in major delays. Hence, the time constraints of thesis

submission did not permit for the full case-control study to be analysed, completed and included in the thesis. However, since permission to access the data has already been granted by the CPRD, the case-control study is planned to proceed following submission of the thesis.

4.3 Results

4.3.1 Summary statistics

A total of 130,105 CYP aged less than 16yrs had a code for mouth ulcers in their CPRD record between January 1st 1990 and December 31st 2019. These were frequency matched by age and sex to a total of 389,929 controls who had no code for mouth ulcers at pseudo-index date. This resulted in an overall total cohort of 520,034 CYP that were studied.

Of the exposed population (CYP with a code for mouth ulcers), 343 subsequently received one of the three systemic disease diagnosis codes of interest (Behcet's, IBD or SLE), after their mouth ulcer code and within the study period. In contrast, only 16 of the unexposed CYP had one of the three systemic disease diagnosis codes dated between their index date and the study end date. In total 359 CYP had an 'outcome' as defined in Section 4.2.4 . Of the 359 outcome codes, 22 were for SLE, 56 for Behcet's, and 281 for IBD. *Figure 6* displays a flow diagram of CYP in the entire cohort detailing their exposure and outcome statuses.

The summary statistics (including sex, index age, ethnicity, IMD group etc.) of the exposed and unexposed populations are presented in *Table 15*. The percentages in this table refer to the proportion of the individual population that number of CYP represents (for example out of 130,105 CYP in the exposed population and 389,929 in the unexposed).

The percentages for ethnicity refer to the proportion of the group with a non-missing ethnic code recorded that was coded under that ethnic group (i.e. out of 6,207 CYP in the exposed group and 257,785 in the unexposed). Again, the percentages for the individual outcomes refer to the proportion the exposed/ unexposed outcome population they represent. There were similar proportions of sexes, ages and index years in the exposed and unexposed populations, as expected in a matched cohort.

A substantially higher proportion of the unexposed population had an ethnicity code recorded (66.7% vs. 4.8%). Of these recorded codes, the proportions of each ethnic group were similar between the exposed and unexposed populations. Each IMD decile was represented approximately equally in each population. The time to diagnosis variable was calculated as the time between index date and first systemic disease code, index date is defined in Section 4.2.3. This was shorter on average in the unexposed population (median 7.3 compared to 8.6 years in exposed). Owing to the lack of data for

ethnicity in the exposed population, ethnicity was not able to be used as an adjustment variable in the later models.

Table 16 displays the summary statistics of the population with any of the 3 outcomes, together and split by diagnosis. The percentages and time to diagnosis were calculated by the same method as in *Table 15*. In the SLE and Behcet's populations there was lower representation of males (4.5% and 39.3%) whereas in the IBD population the proportion of males was higher (56.6%). Ethnicity was poorly coded for in the outcome population (5.6% had data available). Indeed, no CYP with an SLE code had their ethnicity recorded. The IMD deciles of the CYP were approximately evenly distributed in all outcomes.

At diagnosis the median age was similar in all 3 outcomes (17 to 18 yrs.). The highest proportion of CYP in the SLE and Behcet's populations were diagnosed between 16 and 20 yrs. (27.3% and 33.9% respectively), in the IBD population this was between 12 and 16 yrs (24.4%). The oldest diagnosis in this study was made at 39 yrs, and this was of IBD. The median time to diagnosis was longest in IBD at 9.4 yrs, then SLE at 7.2 yrs and finally Behcet's at 5.0 yrs.

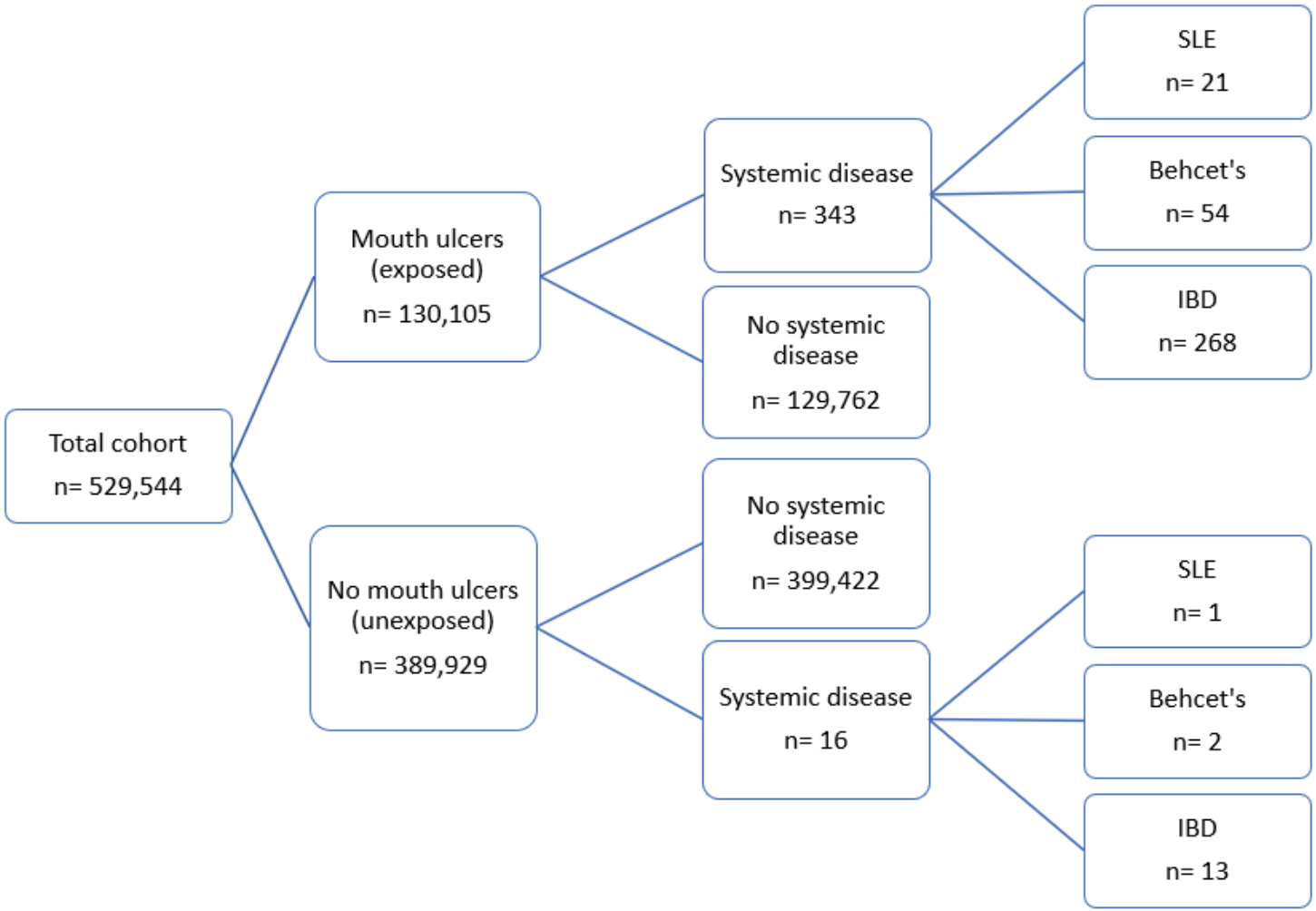

Figure 6- Flow diagram of patients' exposures and outcomes through the study.

- *Total cohort= all CYP included in the study (sum of exposed cases and 3:1 (maximum) matched unexposed cases)*

Table 15- Summary statistics for exposed and unexposed populations (% are of non-missing values)

		Exposed (n=130,105)		**Unexposed (n=389,929)**		**All (n=520,034)**
		n	*%*	n	*%*	n
Sex	**Male**	64,545	*49.6*	193,255	*49.6*	257,800
	Female	65,558	*50.4*	196,674	*50.4*	262,232
	Indeterminate	2	*0.0*	0	*0.0*	2
Ethnicity	**No code recorded**	123,898	*95.2*	132,144	*33.3*	256,042
	Code recorded	6,207	*4.8*	257,785	*66.7*	263,992
	White	4,232	*68.2*	182,632	*70.8*	186,864
	Mixed	189	*3.0*	7,679	*3.0*	7,868
	Asian/Asian British	815	*13.1*	23,099	*9.0*	23,914
	Black/Black British	384	*6.2*	16,600	*6.4*	16,984
	Chinese/Other	145	*2.3*	10,730	*4.2*	10,875
	Not stated/ unknown	442	*7.1*	17,045	*6.8*	17,487
Index age	**Median (yrs)**	5		5		
	Range (yrs)	0-16		0-16		
	Mean (yrs)	6.5		6.0		
	</=4 yrs	59,118	*45.4*	170,214	*43.7*	229,332
	> 4 </= 8 yrs	27,173	*20.9*	118,317	*30.3*	145,490
	>8 </=12 yrs	24,538	*18.9*	94,215	*24.2*	118,753
	>12 </= 16 yrs	19,276	*14.8*	7,183	*1.8*	26,459
IMD deciles	**Range**	1-10		1-10		
	1 (Most deprived)	11,673	*9.0*	38,694	*9.9*	50,367
	2	11,007	*8.5*	35,209	*9.0*	46,216
	3	10,946	*8.4*	35,573	*9.1*	46,519
	4	11,367	*8.7*	35,618	*9.1*	46,985
	5	10,669	*8.2*	36,320	*9.3*	46,989
	6	12,389	*9.5*	38,577	*9.9*	50,966
	7	12,503	*9.6*	41,723	*10.7*	54,226
	8	15,057	*11.6*	43,289	*11.1*	58,346
	9	16,718	*12.9*	43,198	*11.1*	59,916
	10 (Least deprived)	17,776	*13.7*	41,728	*10.7*	59,504

Index year	**1990-1994**	8,787	*6.8*	10,582	*2.7*	19,369
	1995-1999	12,501	*9.6*	37,497	*9.6*	49,998
	2000-2004	20,719	*15.9*	71,568	*18.4*	92,287
	2005-2009	30,060	*23.1*	136,398	*35.0*	166,458
	2010-2014	31,524	*24.2*	91,044	*23.3*	122,568
	2015-2019	26,514	*20.4*	42,840	*11.0*	69,354
Follow up time (years)	**Median**	7.3		10.2		
	Range	0-31.4		0-30.3		
	Mean	8.2		10.3		
Outcomes	**All**	343	*0.3*	16	*0.0*	359
	SLE	21	*6.1*	1	*6.3*	22
	Behcet's	54	*15.7*	2	*12.5*	56
	IBD	268	*78.1*	13	*81.2*	281
Time to diagnosis (all outcomes) (years)	**Median**	8.2		9.3		
	Range	0.03- 28.6		2.9-12.7		
	Mean	8.9		8.9		

Table 16- Summary statistics for populations with outcome codes

		All (n=359)		SLE (n=22)		Behcet's (n=56)		IBD (n=281)	
		n	%	n	%	N	%	n	%
Sex	**Male**	182	*50.7*	1	*4.5*	22	*39.3*	159	*56.6*
	Female	177	*49.3*	21	*95.5*	34	*60.7*	122	*43.4*
Ethnicity	**Not coded**	339	*94.4*	22	*100*	51	*91.1*	266	*94.7*
	Coded	20	*5.6*	0	*0*	5	*8.9*	15	*5.3*
	White	14	*70*	0	*0*	3	*60*	11	*73.3*
	Mixed	0	*0*	0	*0*	0	*0*	0	
	Asian/Asian British	2	*10*	0	*0*	0	*0*	2	*13.3*
	Black/Black British	0	*0*	0	*0*	0	*0*	0	
	Chinese/Other	4	*20*	0	*0*	2	*40*	2	*13.3*
	Not stated/ unknown	0	*0*	0	*0*	0	*0*	0	
Age (index)	**Median**	10		10.5		11		10	
	Range	1-16		2-16		1-16		1-16	
	Mean	9.5		9.8		10.9		9.2	
	</=4 yrs	69	*19.2*	4	*18.2*	6	*10.7*	59	*21.0*
	> 4 </= 8 yrs	76	*21.2*	2	*9.1*	9	*16.1*	65	*23.1*
	>8 </=12 yrs	91	*25.3*	9	*40.9*	18	*32.1*	64	*22.8*
	>12 </= 16 yrs	123	*34.3*	7	*31.8*	23	*41.1*	93	*33.1*
IMD decile	**Range**	1-10		1-10		1-10		1-10	
	1	32	*8.9*	1	*4.5*	7	*12.5*	24	*8.5*
	2	33	*9.2*	2	*9.1*	6	*10.7*	25	*8.9*
	3	26	*7.2*	2	*9.1*	6	*10.7*	18	*6.4*
	4	40	*11.1*	2	*9.1*	5	*8.9*	33	*11.7*
	5	35	*9.7*	2	*9.1*	4	*7.1*	29	*10.3*
	6	40	*11.1*	5	*22.7*	8	*14.2*	27	*9.6*
	7	35	*9.7*	1	*4.5*	6	*10.7*	28	*10.0*
	8	44	*12.3*	4	*18.2*	5	*8.9*	35	*12.4*
	9	33	*9.2*	2	*9.1*	3	*5.4*	28	*10.0*
	10	41	*11.4*	1	*4.5*	6	*10.7*	34	*12.1*

Age (diagnosis)	**Median**	18		17		17		18	
	Range	2-39		9-32		8-34		2-39	
	Mean	18.3		18.6		17.3		18.5	
	</=4 yrs	8	*2.2*	0	*0*	0	0	8	*2.8*
	> 4 </= 8 yrs	9	*2.5*	0	*0*	1	*1.8*	8	*2.8*
	>8 </=12 yrs	50	*13.9*	4	*18.2*	12	*21.4*	34	*12.1*
	>12 </= 16 yrs	84	*23.3*	4	*18.2*	12	*21.4*	68	*24.2*
	>16 </= 20 yrs	88	*24.5*	6	*27.3*	19	*33.9*	63	*22.4*
	>20 </= 24 yrs	60	*16.7*	4	*18.2*	6	*10.7*	50	*17.8*
	>24 </=28 yrs	32	*8.9*	2	*9.1*	3	*5.4*	27	*9.6*
	>28 </= 32 yrs	18	*5.0*	2	*9.1*	2	*3.6*	14	*5.0*
	>32 </=36 yrs	8	*2.2*	0	*0*	1	*1.8*	7	*2.5*
	>36 </=40 yrs	2	*0.6*	0	*0*	0	*0*	2	*0.7*
Year (diagnosis)	**1990-1994**	3	*0.83*	0	*0*	1	*1.8*	2	*0.7*
	1995-1999	11	*3.06*	0	*0*	2	*3.6*	9	*3.2*
	2000-2004	23	*6.39*	3	*13.6*	4	*7.1*	16	*5.7*
	2005-2009	46	*12.78*	5	*22.7*	9	*16.1*	32	*11.4*
	2010-2014	99	*28.33*	5	*22.7*	8	*14.2*	86	*30.6*
	2015-2019	177	*48.61*	9	*40.9*	32	*57.1*	136	*48.4*
Time to diagnosis (years)	**Median**	8.6		7.2		5.0		9.4	
	Range	0.03-28.7		0.6-22.8		0.03-24.3		0.1-28.7	
	Mean	8.9		8.9		6.4		9.4	

4.3.2 Incidence rates and ratios

As seen above in *Table 15*, the exposed population had a higher incidence of outcome (systemic disease) codes than the unexposed population: 0.26% vs 0.004%. There were 343 cases of systemic disease in the exposed population compared to 16 cases in the unexposed population. In total, the 13,105 exposed patients contributed 1,129,850 person-years to the study hence the combined incidence rate for all three systemic diseases was 30.4 (CI:27.2-33.8) per 100,000 person-years. In comparison there were 16 cases of systemic disease in the 389,929 unexposed patients who contributed a total of 4,0193,33 person-years. Hence the combined incidence rate of all three systemic diseases in the unexposed population was 0.4 (CI:0.2-0.7) per 100,000-person years. The incidence rate ratio (IRR) between the exposed and unexposed population was 73.7 (CI: 46.2-125.9), before adjustment. The rate difference for all three systemic diseases was 30 (CI:26.7-33.2) per 100,000 person-years.

Individually, each systemic disease had a higher incidence rate in the exposed population compared to the unexposed. In the exposed population, there were 21 cases of SLE recorded, with the same contribution of person-years as reported above, the incidence rate was 1.9 (CI:1.2-2.8) per 100,000 person-years compared to 1 case of SLE in the unexposed population and hence an incidence rate of 0.02 (CI:0-0.14) per 100,000 person-years. The IRR for SLE in the exposed compared to the unexposed population was 74.7 (CI:10.1-555.3), with an absolute rate difference of 1.8 (CI:1.2-2.6) per 100,000 person-years. There were 54 cases of Behcet's in the exposed population and 2 case in the unexposed population, resulting in incidence rates of 4.8 (CI:3.6-6.2) per 100,000 person-years and 0.05 (0.01-0.18) per 100,000 person-years respectively. The IRR for Behcet's disease was 96 (CI:23.4-394)) when exposed and unexposed populations were compared, the absolute rate difference was 4.7 (CI:3.6-6.0). The occurrence of IBD in the exposed population was 268 cases with a rate of 23.7 (CI:21-26.7) compared to 13 cases in the unexposed population with a rate of 0.3 (CI:0.2-0.6). The IRR for IBD was 73.3 (CI:42-128) with an absolute rate difference of 23.49(CI:10.6-26.2). These results are presented in *Table 17*.

4.3.3 Modelled incidence rate ratios

Table 18 shows the IRRs modelled using the Poisson regression model, with adjustment for multiple variables. The model was initially run with no adjustment, then adjusted for age and sex, then IMD decile was added as an adjusting variable. All models were offset for the person-years contributed to the study by each individual. The IRR for all three systemic diseases combined was 73.7, which was the same in both adjusted models. The IRR was also 73.7 in all models with IBD as the outcome and in

the unadjusted and age and sex adjusted model for SLE. There was variation in confidence interval between some models. In the SLE model adjusted for age, sex and IMD, the IRR was 66.7 (CI:14.9-1212.0). Finally, the unadjusted IRR for Behcet's as the outcome was 99.5 (CI:30.0-601.8), which again replicated in the model adjusted for age and sex, when IMD was added as an adjustment the IRR became 90.0 (CI: 27.1-544.6).

Table 17- Incidence data for all and each systemic disease

	All systemic diseases		**SLE**		**Behcet's**		**IBD**	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**	**Exposed**	**Unexposed**
N	130,105	389,929	130,105	389,929	130,105	389,929	130,105	389,929
Person-years	1,129,850	4,019,333	1,129,850	4,019,333	1,129,850	4,019,333	1,129,850	4,019,333
Outcome (n)	343	16	21	1	54	2	268	13
Per 100,000 person-yrs	30.4 (27.2-33.8)	0.4 (0.2-0.6)	1.9 (1.2-2.8)	0.02 (0-0.14)	4.8 (3.6-6.2)	0.05 (0.01-0.18)	23.7 (21-26.7)	0.3 (0.2-0.6)
Incidence rate ratio	76.2 (46.2-125.9)		74.7 (10.1-555.3)		96 (23.4-394)		73.3 (42-128)	
Rate difference (per 100,000 person-yrs)	30 (26.7-33.2)		1.8 (1.2-2.6)		4.7 (3.6-6.0)		23.4 (10.6-26.2)	

Table 18- Unadjusted compared to adjusted incidence rate ratios for all and each systemic disease

		Outcome (n)	Person-yrs	Unadjusted IRR (CI)	Adjusted IRR (CI) for age and sex	Adjusted IRR (CI) for age, sex and IMD
All systemic diseases	Exposed	343	1,129,850	73.7 (49.4-134.3)	73.7 (49.4-134.3)	73.7 (44.7-121.5)
	Unexposed	16	4,019,333	1 ()	1()	1()
SLE	Exposed	21	1,129,850	73.7 (14.9-1339.4)	73.7 (16.4-1339.4)	66.7 (14.9-1212.0)
	Unexposed	1	4,019,333	1()	1()	1()
Behcet's	Exposed	54	1,129,850	99.5 (30.0- 601.8)	99.5 (30.0- 601.8)	90.0 (27.1-544.6)
	Unexposed	2	4,019,333	1()	1()	1()
IBD	Exposed	268	1,129,850	73.7 (44.7- 134.3)	73.7 (44.7- 134.3)	73.7 (44.7- 134.3)
	Unexposed	13	4,019,333	1()	1()	1()

4.3.4 Stratified incidence rate ratios

The Poisson model was also applied to various sub-populations of the cohort, stratified by sex, index age and IMD. The models for age stratified groups were adjusted for sex and IMD, the models for sex stratified groups were adjusted for age and IMD, and the models for IMD stratified groups were adjusted for age and sex. In all stratified groups a code for mouth ulcers at less than 16 years old increased the risk of a systemic disease code later in life. These results are displayed in *Table 19.*

The data demonstrated that the female population had a slightly higher IRR than the male population (81.5 (CI:44.7-181.3) vs 60.3 (CI:33.1-244.7)), although there is no evidence of a statistically significant difference.

The IRR for age (associated with the presence of mouth ulcers in relation to systemic disease diagnosis) showed no discernible trend, and all confidence intervals overlapped. This suggests that mouth ulcer exposure associated with the risk of systemic disease diagnosis was not affected by the age of CYP in this cohort.

IMD decile appears to make some contribution to the effect of mouth ulcers on the risk of systemic disease: as IMD level decreases, the IRR also decreases suggesting that a lower level of deprivation decreases the risk of systemic disease associated with mouth ulcers. Again, there are overlapping confidence intervals which would suggest that this trend may not be significant clinically.

Table 19- Poisson regression model results for various sex, age and IMD group sub-populations, in relation to mouth ulcers as the primary exposure

Stratified variable	Person-yrs	Outcomes	IRR	Confidence interval
Male	2,578,548	182	60.3	(33.1-134.3)
Female	2,572,713	177	81.5	(44.7-181.3)
Index age </=4 yrs	1,574,735	70	73.7	(33.1-244.7)
Index age >4 </=8 yrs	1,583,512	75	60.3	(49.4-148.4)
Index age >8 </=12 yrs	1,694,078	92	73.7	(33.1-221.4)
Index age >12 </=16 yrs	298,936	123	4.9 x10^8	(1-inf)
IMD High (deciles 1/2)	1,132,809	65	6.5 x10^9	(1-inf)
IMD MedHigh (3/4)	1,120,447	66	121.5	(44.7-492.7)
IMD Med (5/6)	984,894	75	60.3	(22.2-244.7)
IMD MedLow (7/8)	948,015	79	33.1	(13.4-109.9)
IMD Low (9/10)	965,096	74	11.0	(4.5-30.0)

4.3.5 Ethnicity as a variable

Ethnicity was not included as a variable in the Poisson regression model due to the potential of paucity of the ethnicity data to skew results. Only 4.4% of CYP with mouth ulcers had their ethnic group recorded compared to 66.1% of CYP without mouth ulcers, hence running an analysis model on this data would be inappropriate due to the clear bias in the completeness of data.

4.4 Discussion

4.4.1 Key findings

A code for mouth ulcers in the primary care record of CYP aged less than 16 years old significantly increased the risk of subsequent systemic disease diagnosis. The incidence rate ratio for all three systemic diseases combined was 76.2 (CI:46.2-125.9). The risk of each systemic disease individually was also increased in the population of CYP with mouth ulcer codes compared to the population without. The incidence rate ratios were: 74.7 (CI:10.1-555.3) for SLE; 96 (CI:23.4-394) for Behcet's; and 73.3 (CI:42-128) for IBD. Adjustment for sex, age and IMD did not make a significant difference to the risk. Although the

risk was significantly increased in each and all systemic diseases, the absolute risk was still small as demonstrated by the rate difference which ranged from 1.8-30.

4.4.2 Strength and limitations

4.4.2.1 Representativeness

Data in the CPRD database is representative of the UK population as a whole, the data in this study was from England only due to the IMD data linkage however there is no reason to believe there would be differences between UK countries. Notably, there was an even distribution of exposed CYP across the IMD deciles reflecting them to be representative of the general UK population. Hence it can be expected that any trends in demographics of the data are due to other factors in the study such as patient selection, the nature of the exposure and outcomes, or coding behaviours of GPs.

The unexposed population was selected based on a sampling frame created from the age and sex proportion in the exposed population, meaning each case did not have an exact matching counterpart to compare to. This method is typical of a cohort study. However, in this context it resulted in index dates for the unexposed population that did not exist in their record since the median index date of that group was used (further explained in *Section 2.6*). Additionally, the CPRD only provides the year of birth for patients, not exact date of birth, hence ages in both groups are estimates based off this data. It is not considered necessary to individually match participants of a cohort study to assess the differences in contribution (to outcome risk) of age and sex distribution. In any case age and sex did not alter the value of the IRR for systemic disease diagnosis when adjusted for in this study even though the models adjusting for age and sex fit better for systemic diseases collectively as an outcome as well as Behcet's individually.

In terms of age at diagnosis, the median age was 18 years ranging from 2 to 39 years (*Table 16)*. The follow up time in this study gives a theoretical exclusion age of greater than 45 years at diagnosis, for example if a CYP was 15 on the first day of the study and remained in the study for the full 30 years of follow up. Hence the results may be biased towards patients diagnosed in childhood and/or the early to mid-adulthood. This must be considered when assessing results of the study, particularly the effect of mouth ulcers at an age of less than 16 years.

4.4.2.2 Recording of exposure

General limitations of CPRD data in recording of clinical data that apply in this study include: definitions of disease are not standardised for each diagnosis and a code relies upon clinician's judgement for

accuracy, unlike in other studies where accepted diagnosis/classification criteria may be used. Code lists in this study were verified by experienced clinicians to ensure applicable codes were searched for however the use of these codes may have been inconsistent when inputted into the patient's record at primary care level.

Mouth ulcers in CYP are rarely severe enough to warrant intervention in secondary care, thus using a primary care data source to define a cohort of CYP with mouth ulcers is appropriate in the context of this study. Data are entered into the primary care records for the purposes of record keeping in routine consultation, not specifically for research, and so only those signs, symptoms and diagnoses that are deemed relevant by the GP are likely to be coded. It is therefore likely that there will be a coding bias with only the more severe mouth ulcers being coded in a CYP's record. We identified as broad a set of codes to represent mouth ulcers (*see appendix D*) to try and capture as many patients as possible who had had a code for mouth ulcers. In addition, we cannot examine the influence of health-seeking behaviour with the distinct possibility that many children who do have (severe) mouth ulcers will not present to primary care as their condition may resolve without further input from healthcare professionals / intervention.

Nonetheless, these results reflect a population of children who have presented at the GP with mouth ulcers that warrant recording in their general practice data. They have shown a significant association with future incidence of systemic disease compared with children without a recording of mouth ulcers.

With regard the three conditions of interest in this study, mouth ulcers as a symptom may well have been overshadowed by other more significant symptoms (in the view of the practitioner) and hence a Read code may not be inputted. For example, the systematic review would suggest that: in SLE, joint or renal involvement and malar rash are typically present; whereas in IBD., gastrointestinal symptoms would be expected such as abdominal pain, diarrhoea and perianal signs; and in Behcet's, specific skin lesions, genital ulcers and ocular symptoms may be of more concern. In SLE and IBD mouth ulcers are often present but other symptoms take priority in coding data, whereas in Behcet's mouth ulcers are often the most significant early symptom, compared to a typically subtle skin rash for example. Also, a CYP presenting with genital ulcers or ocular involvement are unlikely to been seen by a GP without specialist referral, particularly as GPs will not diagnose ocular involvement as CYP require ophthalmology review. Additional time would have permitted other presenting symptoms and/or clusters of symptoms to be assessed in a case-control study of CPRD data, this is discussed below.

4.4.2.3 Recording of outcome

The rate ratios in this study do not represent the systemic disease occurrence of a CYP with mouth ulcers in the general population, they represent the incidence of systemic disease code in a CYP who has troublesome enough mouth ulcers that they have presented to primary care and that a physician has inputted a code for, Particularly in CYP, the three conditions of interest are usually diagnosed in secondary or tertiary care settings. It is highly likely that systemic disease diagnosed in secondary care would be inputted into the primary care record, however exposure would not affect the method used by secondary care to communicate diagnoses back to primary care (typically via letter to a GP) hence, if there was information bias, it is likely equal in both groups.

There can be issues with follow up in the CPRD database which may affect the likelihood of a participant receiving an outcome code: the CPRD does not have the ability to link patient's records if they move practices hence the data chain is terminated and a new chain is commenced. This means follow up from childhood to adulthood, as required in this study, can be difficult in CPRD data hence some outcome cases may have been missed in this study. However, as we censored individuals at their time of exit from the study we have been consistent with exposed and unexposed children. There is no reason to expect that there is more movement in the exposed or unexposed group, so this is unlikely to have materially affected the results. As seen in *Table 15* the median follow-up time was shorter in the exposed group: 7.3 years in the exposed participants compared to 10.2 years in the unexposed. However, this is likely due to more of the exposed participants acquiring a diagnosis and hence leaving the study rather than differences in movement.

4.4.2.4 Availability of data for covariates

Internal and external quality measures, within the CPRD process, ensure that included data is accurate and hence researchers can trust the initial data source for their analysis. For example the Quality and Outcomes Framework (QOF) introduced in 2004 improved completeness of records in the following years (163). However, this study has highlighted that missing data can still be an issue particularly in terms of ethnicity data. Missing data could have been driven by data collected prior to 2004 in this study. Ethnicity was particularly poorly coded for in the population of CYP with mouth ulcers, which was unexpected since these are the CYP with a known healthcare contact hence it would be assumed that they would have a higher chance of obtaining an ethnicity code in their primary care record.

The relationship between mouth ulcers, risk of systemic disease and ethnicity could not be reliably determined due to the very small number of CYP with outcome codes that also had ethnicity data available. Attempts were made to reduce the effect of missing data on the results, for example removing ethnicity as a covariate in the statistical model for adjustment.

All patients had date of birth, sex and IMD data available, as dictated by CPRD patient acceptability flags and/or the inclusion criteria of this study. IMD is a geographic variable that is applied at an individual level; hence this study assumes the deprivation level of individual CYPs based on their location which could be inaccurate in some cases. However, there is no demonstrable difference in incidence rate ratios in those with mouth ulcers compared with not by IMD so ecological fallacy did not affect the results of the study.

4.4.2.5 Size

The overriding benefit of analysing CPRD data is the breadth and size of the data. There are over 79 million person-years accounted for within the database(163), hence statistical precision is greater compared to using smaller datasets such as those collected by individual researchers. The large data pool was particularly necessary in terms of the rare outcomes that have been assessed. However, because the outcomes assessed in this study were rare and large confidence intervals were observed around point estimates of measures of effect.

4.4.3 Comparison with previous literature

There are no previously available data for incidence rates or ratios of these three conditions combined together, as there are no published studies that have reviewed all three as collective 'systemic diseases.' There is also no current literature assessing the risk of development of SLE, IBD or Behcet's in CYP with mouth ulcers in any context. However, the demographic data in this study can be compared to what is currently known about mouth ulcers and these systemic diseases.

There were roughly similar proportions of females in CYP with mouth ulcers. The age distribution of CYP with mouth ulcers in this study is in contrast to the previously published and accepted peak prevalence of 10 to 19 years(4). The median age of the population with mouth ulcers in this cohort was 5 years, with 45% of them aged </= 4 years. Ethnicity cannot be commented on due to the limited data availability.

In terms of outcomes, data summarised in *Table 16* demonstrates that there were more females in the SLE and Behcet's outcome categories, whereas there were more males in the IBD group. The distribution is typical in SLE as it is widely recognised that there is a greater incidence in females compared to males in this condition(164). In a typical Behcet's population a fairly even distribution of sexes would be expected, however a marginally higher percentage of females has been reported in the UK paediatric age group(6). In a typical IBD population there would be more females than males(165). There were small numbers of cases in all three categories and hence the distribution data should not be relied upon to portray the general distribution of each disease. Some of the discrepancies with the accepted distribution of the disease could be explained by other factors in the study population such as age and health seeking behaviours.

This study analysed a 30-year period between 1990 - 2019 and required an age of less than 16yrs at index for inclusion. Therefore, the oldest age at which a diagnosis could be theoretically made and included in this study is 45 yrs (e.g. if a young person entered the first year of the study at aged 15yrs and was diagnosed within the last year of the study). Hence, any diagnosis made in adulthood after the age of 45 years would not have been included in this study and therefore the results will be skewed towards the lower incidence rate as in the paediatric population. It is difficult to predict exactly the expected incidence rate in this cohort of mixed paediatric and adult patients in order to compare the incidence rate in the exposed population.

The incidence rate of SLE codes in the exposed group was 1.9 (CI:1.2-2.8) per 100,000 person-years, whereas the unexposed group the incidence was 0.02 (CI:0-0.14) per 100,000 person-years. The most recent estimate of incidence of SLE in the UK is between 4.7 and 5.1 per 100,000 person-years (166) for adults and between 0.4 and 0.5 per 100,000 person-years (8) in CYP. Hence the exposed group in this study had a lower incidence than would be expected in an adult population, but higher incidence than that of a paediatric population. As shown in *Table 16,* 36% of SLE diagnoses were made at an age </= 16 years whereas the remaining cases were diagnosed during adulthood. Hence it would concur that the incidence rate in this group would fall between the expected incidence rates in adulthood and childhood. However, the incidence rate ratio of 74.7 (CI:10.1-555.3) would suggest that CYP with a mouth ulcer code were more likely to receive an SLE diagnosis in this study, compared to those without.

The exposed population in this study had an incidence of Behcet's cases of 4.8 (3.6-6.2) per 100,000 person-years compared to 0.05 (0.01-0.18) per 100,000 person-years in the unexposed population. 45% were diagnosed at less than 16 years old so, as previously described, it would be expected that the

incidence rate would fall somewhere between the estimate for adult and paediatric populations. The current estimates of incidence rate of Behcet's disease is 0.1 per 100,000 person-years in CYP under the age of 16yrs (6), and 0.2-0.6 per 100,000 person-years in adults in the USA (167). These figures are the most accurate estimates for the two age groups, despite geographical variation, due to the rarity of Behcet's disease. It is evident that the incidence rate of Behcet's disease in the patients with a code for mouth ulcers during childhood in this study was considerably higher than the expected incidence rate in the general paediatric and adult population. Hence it could be concluded that Behcet's disease is more common in CYP with mouth ulcers, and therefore they are at higher risk of Behcet's disease. Also, a large proportion of Behcet's disease cases could be said to begin with a primary care code for mouth ulcers at age </= 16 years, since the incidence rate is dramatically less in the general population compared to the population of CYP with mouth ulcers. The aforementioned risk of a skew in the incidence rate of CYP with SLE towards the paediatric incidence rate, may be less evident in the Behcet's population since most diagnoses are made between ages 25 and 30 years. This is within the maximum age at diagnosis of this study (45 years). It could be hypothesised that most juvenile and adult- onset cases of Behcet's disease were captured in this study. As in SLE, the incidence rate ratio for Behcet's disease comparing the CYP with and without mouth ulcer codes (96 (CI:23.4-94)), would suggest that a Behcet's disease diagnosis was more common in CYP with a mouth ulcer code.

The incidence rate of IBD in the CYP with mouth ulcer codes was 23.7 (CI:21-26.7) per 100,000 person-years, compared to 0.3 (CI:0.2-0.6) per 100,000 person-years in the CYP without mouth ulcers. The current incidence estimate of paediatric IBD is 10.5 cases per 100,000 person-years(10), compared to the adult estimate 68.6 to 78.4 IBD cases per 100,000 person-time years(168). As in SLE, the incidence in the exposed population of this study falls between that of the paediatric and adult incidence estimates. This could be for the same reasons as stated above: 42% of patients were diagnosed at </=16 years so there were both adult and paediatric cases in this study; and peak prevalence of IBD in adulthood occurs at an age greater than 45 years (165) so some cases diagnosed in adulthood may have been missed due to the length of this study. Furthermore, the incidence rates above are the most recent published figures and research suggests that, particularly in paediatric cases(10), incidence of IBD increased across the period of this study (1990 to 2019). Therefore, the incidence rates (in the exposed and unexposed populations) may have been skewed by the increasing incidence of IBD in the general population during the study period. Although an estimate to predict expected incidence rate in this population is difficult, the incidence rate ratio of 73.3 (CI:42-128) would suggest that there was a higher number of codes for IBD diagnoses in the CYP with mouth ulcer codes compared to those without mouth ulcer codes.

The incidence rate ratio data (*Table 17*) is representative of current clinical understanding in that the largest ratio between CYP with and with mouth ulcers is in Behcet's disease, followed by SLE and IBD: it is known that a typical presentation profile in Behcet's will include mouth ulcers whereas other symptoms are more common in IBD and SLE. This experience is also supported by the systematic review in that studies reported higher frequencies of mouth ulcers at onset in Behcet's populations compared to SLE and IBD populations. In addition, other symptoms are typically more severe in SLE and IBD hence a mouth ulcer is less likely to be coded for as the clinician's focus may be diverted to the symptoms causing the most issues, as discussed above (*Section 4.4.2.2*).

4.4.4 Relevance to wider clinical / public health context

As discussed above, based on the data arising from this study to date, it would be inappropriate to directly inform patients and parents of the specific risk their child might subsequently have of developing one of these three systemic diseases, based solely on data arising from this study before it is validated in other contexts. Limitations noted here in the study mean that it may give a misrepresentation of the actual risks associated. The general consensus of the PPIE participants would concur with this.

The median time to diagnosis was 8.3 years, from first mouth ulcer code, which suggests there is an opportunity for identification and earlier diagnosis or potentially intervention. However, the relative risk of systemic disease diagnosis is still low in CYP with a mouth ulcer code because these three conditions are rare: of 100,000 person years of follow up after mouth ulcers there were only approximately 30 cases of systemic disease. This implies that active follow up of people with mouth ulcers is unlikely to be an effective clinical tool to identify and diagnose systemic disease at an earlier stage, further research would be required to validate this.

Since this study used CPRD data, the findings can only be applied to a UK primary care population with any validity. Considering this, the results may be beneficial for educating primary care physicians in terms of the need for referral to specialist services in CYP at risk of systemic diseases, as defined by this study. It has also been highlighted the need for protocols to ensure GPs input ethnicity codes for their patients. Lacking ethnicity data was also an issue highlighted by the systematic review in currently published studies, hence it may be a universal issue in research generally.

4.4.5 Further research

4.4.5.1 CPRD Case-control study

The proposed CPRD case-control study originally planned to be included in this thesis would add further context to the results of this cohort study. It will analyse CPRD data for previous mouth ulcer codes (and potentially clusters of other presenting symptoms) in a population of CYP with a diagnosis of SLE, Behcet's or IBD, and a matched control population without. This should provide a larger number of outcome cases which will increase the power of the results of the study and mitigate the limitations of this study with regards to a limited outcome population. The two studies combined will be more able to answer the question: 'Are CYP with mouth ulcers at a higher risk of systemic diseases such as SLE, Behcet's and IBD?'. However, this will still be in the context of CPRD data and the previously discussed limitations of using this type of data will still apply.

4.4.5.2 Beyond CPRD data

As highlighted in the systematic review, further research is required on this topic as these two studies alone will not fill the gap in current literature. A study is required outside of the context of CPRD data (UK primary care) in order to determine if the results found here are applicable to the general paediatric population. Also, an international perspective is required as these study results may not apply to populations outside of the UK, especially due to the known ethnicity distribution in some of the systemic diseases. To fully answer the question a prospective study of a large, representative, international cohort of CYP is required to determine if mouth ulcers can be considered a valid predisposing factor for systemic disease diagnosis. Only then would it be acceptable to inform patients and parents of the findings in clinical practice.

4.5 Key Findings

In summary, the key findings from this CPRD cohort study include:

- The incidence rate of any of the three systemic diseases was considerably higher in the CYP with mouth ulcers coded for in their record, compared to those without.
- Adjustment for sex, age and IMD did not considerably affect the risk of systemic disease diagnosis in CYP with mouth ulcers.

- Ethnicity data was poorly coded for in this cohort. Primary care practices that provide data to the CPRD require protocols to ensure physicians input ethnicity codes.
- A further case-control study of CPRD data would is the next step in assessing the odds of prior diagnosis of mouth ulcers in CYP with systemic disease. Future prospective studies are also required to provide a general population and international perspective.

4.6 Conclusions

This study is the first step in 'Assessing the risk of systemic diseases, such as Behcet's, SLE and IBD, in CYP that have a code for mouth ulcers in their primary care record'. It was able to show that CYP in this study with a code for mouth ulcers were at a higher risk of subsequently receiving a systemic disease code. It also raised further discussion points that could be validated by the next step: a case-control study using the CPRD database.

5 Chapter 5: Discussion and Conclusions

This thesis sought to understand the risk of developing a serious systemic inflammatory condition in CYP who present with mouth ulcers. The systematic review of the existing literature (*Chapter 2*) aimed to determine the current evidence base for the outcomes of CYP with mouth ulcers, specifically their risk of developing a systemic disease following a presentation of mouth ulcers to a healthcare setting. It found that no current published literature assesses the risk of systemic disease, in children who present to a healthcare setting with mouth ulcers, and that within this literature the focus is on tertiary care settings.

The programmed of PPIE research (*Chapter 3*) aimed to inform the subsequent CPRD study, including how results and outcomes are presented. The findings highlighted that care should be taken when applying the results of the CPRD study to clinical practice. However, points raised by CYP in all stages of PPIE research supported the proposed primary outcome of the CPRD cohort study. Some consensus was reached as to the language to be used in the CPRD study findings however there were some discrepancies due to personal preference and lived experience.

Finally, the CPRD cohort study (*Chapter 4*) aimed to determine the risk of developing a serious systemic inflammatory condition in CYP who present with mouth ulcers in a primary healthcare setting. The results of this study were that the incidence rate of SLE, Behcet's and IBD were all considerably higher in the CYP with mouth ulcers coded for in their record, compared to those without mouth ulcers: 30.4 (CI: 27.2-33.8) compared to 0.4 (CI:0.2-0.6) per 100,000 person-years. These data therefore suggested that CYP who present to primary care with mouth ulcers are at a significantly increased risk of subsequent systemic disease diagnosis, as supported by the calculated IRRs.

5.1 Discussion

The initial literature review identified that there were no current literature assessing the risk of systemic disease, specifically SLE, Behcet's or IBD, in children who present to a healthcare setting with mouth ulcers. Hence it was concluded that a study to assess this risk would be beneficial to the current knowledge base. The literature review was able to provide key variables, in addition to the main outcome of risk, to focus the analysis of the proposed study on: clusters of non-mouth ulcer presenting symptoms, time lag from presentation to diagnosis, association with age, sex and ethnicity.

Since no reviewed literature was based in primary care it was concluded that the proposed study should utilise primary care data to gratify some of the gaps in current knowledge. Also, primary care is where children with mouth ulcers present to, and there is no secondary or tertiary care database as long standing/robust as the CPRD. Originally a cohort and case-control study of the CPRD was proposed, however due to unexpected delays in the data extraction and analysis during the cohort study, the case-control study was not deemed possible within the time constraints of this thesis. The cohort study was not able to assess non-mouth ulcer symptoms as identified above, however the proposed case-control study will be able to address this aim in the future.

During the cohort study design phase and following data analysis, PPIE input was sought to further inform the study in addition to information the literature review had provided. The proposed outcome, an IRR to determine risk of systemic disease diagnosis in CYP with mouth ulcers in primary care, was evaluated by various groups of CYP, patients and parents. In all phases of PPIE input there was positive feedback on the proposed outcome, for example reassurance was believed to be a key component of quantifying risk for patients and parents. Other points raised included provision of preparation time, raising awareness of rare conditions in childhood and patient/parent validation of symptoms. Responses in all phases highlighted that the outcome would be most beneficial if the risk of systemic disease could be reduced or delayed. Further research would be required to assess if earlier intervention, given risk calculations, could affect the subsequent disease course in any of the three conditions.

Some concerns were raised as to the mental health impact on CYP and their families of raising concerns regarding potential risk arising from having mouth ulcers, which was deemed unnecessary in CYP that would not eventually receive the 'at risk' diagnosis. Thus, care must be taken when applying the results of the cohort study to clinical practice. For example, the IRR could be used as an education tool for primary care physicians rather than informing patients and parents of risk directly. Discussions around acceptable language to CYP and their parents were used to inform the presentation of the CPRD cohort study results.

In the CPRD cohort study, the incidence rate of any of the three systemic diseases was considerably higher in the CYP with mouth ulcers coded for in their record (30.4 per 100,000 person-years), compared to those without (0.4 per 100,000 person-years). These data therefore confirmed the long-held clinical suspicion that children with mouth ulcers are typically at higher risk of SLE, IBD or Behcet's disease. Adjustment for sex, age and deprivation level did not considerably affect the risk of systemic disease diagnosis in CYP with

mouth ulcers, suggesting that these factors do not make significant contribution to risk in this scenario. Although it was initially planned to adjust for ethnicity, given the findings of the literature review, data was poorly coded for in this cohort. Thus, it was concluded that primary care practices may need to improve the coding of ethnicity.

Overall, the CPRD cohort study found that the absolute risk of SLE, Behcet's or IBD in CYP was low, despite the considerably increased risk in CYP with mouth ulcers. The systematic review found that the specificity of mouth ulcers was also low. Hence, as suggested in the PPIE input, this research could be used to raise awareness of the diagnosis of these three conditions which are rare in CYP, rather than to predict which CYP may receive diagnoses. This would ideally prevent some of the mental health concerns raised by PPIE input.

5.2 Implications and future research

This thesis has identified a gap in the current literature relating to the risk of subsequent systemic disease diagnosis in CYP with mouth ulcer. The results of the CPRD cohort study were able to partially address this gap in the UK primary care setting. Although CYP and parents felt that applying this knowledge to clinical practice was helpful in some respects, care must be taken as not to negatively impact the mental health of patients/parents thus a professional education approach may be more acceptable. For example, through an alert on GP electronic systems that appears when mouth ulcers are coded for and highlights the increased risk of systemic disease. Or presentations to be incorporated into GP training programmes.

There is still a gap in the literature relating to how clusters of other presenting symptoms may be associated with the risk of systemic disease in CYP with mouth ulcers, the proposed case-control study would be able to contribute to this, again through analysis of the CPRD database. The CPRD cohort and case-control studies combined would provide large dataset results which would add to current knowledge, however only in the context of UK primary care.

To fully assess the risk of SLE, IBD and Behcet's in all CYP with mouth ulcers, an international, prospective study would be required. It would be able to analyse the contribution of age, sex, ethnicity, deprivation level, other presenting symptoms and time lag in a cohort of CYP from the international, general population. Issues may arise with this approach including loss to follow up and maintaining protocol

methods internationally. Studies of the CPRD database may be more clinically relevant because they assess the risk in a setting where earlier intervention may be possible.

5.3 Conclusions

This thesis identified important gaps in the existing literature relating to the risk of systemic disease in CYP with mouth ulcers presenting to a healthcare setting. This paucity of data underpinned the importance of undertaking a robust cohort study of CPRD data, which was formulated and conducted on the basis of this evidence, and importantly, informed by insights and perspectives provided through the three phases of PPIE investigation. The study concluded overall that children receiving a mouth ulcer code on CPRD, following consultation in primary care, are at higher risk of a subsequent systemic disease diagnosis. Areas for further research on this topic were identified in all three stages of the study design.

6 References

1. Park N. Population estimates for the UK, England and Wales, Scotland and Northern Ireland, provisional: mid-2019. Hampshire: Office for National Statistics. 2020.
2. Légeret C, Furlano R. Oral ulcers in children- a clinical narrative overview. Italian Journal of Pediatrics. 2021;47(1):144.
3. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic Features of Common Oral Ulcerative Lesions: An Updated Decision Tree. Int J Dent. 2016;2016:7278925-.
4. Plewa MC. Pediatric Aphthous Ulcers [Online article]. Medspace online: Medspace.com; 2019 [updated 25/02/2019; cited 2021 22 Oct.]. Available from: https://emedicine.medscape.com/article/909213-overview#a6.
5. Yıldız M, Köker O, Adrovic A, Şahin S, Barut K, Kasapçopur Ö. Pediatric Behçet's disease - clinical aspects and current concepts. Eur J Rheumatol. 2019;7(Suppl 1):1-10.
6. Pain CE, Beresford MW, Fortune F, Lai ETC, Murphy R, Taylor-Robinson D, et al. Behçet's syndrome in children and young people in the United Kingdom and the Republic of Ireland: a prospective epidemiological study. Rheumatology (Oxford). 2021;60(10):4728-36.
7. Levy DM, Kamphuis S. Systemic lupus erythematosus in children and adolescents. Pediatr Clin North Am. 2012;59(2):345-64.
8. Lythgoe H, Smith EMD, Killeen OG, Murphy R, Pilkington C, Pain CE, et al. Prospective epidemiological study of juvenile-onset Systemic Lupus Erythematosus in the United Kingdom and Republic of Ireland. Rheumatology (Oxford). 2022.
9. Sandhu BK, Fell JM, Beattie RM, Mitton SG, Wilson DC, Jenkins H. Guidelines for the management of inflammatory bowel disease in children in the United Kingdom. J Pediatr Gastroenterol Nutr. 2010;50 Suppl 1:S1-13.
10. Ashton JJ, Cullen M, Afzal NA, Coelho T, Batra A, Beattie RM. Is the incidence of paediatric inflammatory bowel disease still increasing? Archives of Disease in Childhood. 2018;103(11):1093.
11. Ye Y, Manne S, Treem WR, Bennett D. Prevalence of Inflammatory Bowel Disease in Pediatric and Adult Populations: Recent Estimates From Large National Databases in the United States, 2007–2016. Inflammatory Bowel Diseases. 2019;26(4):619-25.
12. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J Eur Acad Dermatol Venereol. 2014;28(3):338-47.
13. Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, de Ridder L, et al. ESPGHAN Revised Porto Criteria for the Diagnosis of Inflammatory Bowel Disease in Children and Adolescents. Journal of Pediatric Gastroenterology and Nutrition. 2014;58(6).
14. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.
15. Agency MHpR. Clinical Practice Research Datalink: NIHR; 2022 [Available from: https://cprd.com/.
16. Group OLoEW. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine.2011. p. https://www.cebm.net/.
17. Bahabri S, Sabban EA, Al Rashed A, Al-Mayouf S, Al Mazyed A, Abdulrazik A, et al. Juvenile systemic lupus erythematosus in 60 Saudi children. Ann Saudi Med. 1997;17(6):612-5.

18. Mok CC, Mak A, Chu WP, To CH, Wong SN. Long-term survival of southern Chinese patients with systemic lupus erythematosus: a prospective study of all age-groups. Medicine (Baltimore). 2005;84(4):218-24.
19. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore). 1993;72(2):113-24.
20. Font J, Cervera R, Espinosa G, Pallarés L, Ramos-Casals M, Jiménez S, et al. Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. Annals of the rheumatic diseases. 1998;57(8):456-9.
21. Chiang L-L, Lin Y-T, Chan H-Y, Chiang B-L. Differential manifestations of prepubescent, pubescent and postpubescent pediatric patients with systemic lupus erythematosus: A retrospective study of 96 Chinese children and adolescents. Pediatric Rheumatology. 2012;10(1):12.
22. Nazri S, Wong KK, Hamid W. Pediatric systemic lupus erythematosus. Retrospective analysis of clinico-laboratory parameters and their association with Systemic Lupus Erythematosus Disease Activity Index score. Saudi Med J. 2018;39(6):627-31.
23. Uziel Y, Gorodnitski N, Mukamel M, Padeh S, Brik R, Barash J, et al. Outcome of a national Israeli cohort of pediatric systemic lupus erythematosus. Lupus. 2007;16(2):142-6.
24. Zhu J, Wu F, Huang X. Age-related differences in the clinical characteristics of systemic lupus erythematosus in children. Rheumatol Int. 2013;33(1):111-5.
25. Iqbal S, Sher MR, Good RA, Cawkwell GD. Diversity in presenting manifestations of systemic lupus erythematosus in children. J Pediatr. 1999;135(4):500-5.
26. Bader-Meunier B, Armengaud JB, Haddad E, Salomon R, Deschênes G, Koné-Paut I, et al. Initial presentation of childhood-onset systemic lupus erythematosus: a French multicenter study. J Pediatr. 2005;146(5):648-53.
27. Hiraki LT, Benseler SM, Tyrrell PN, Hebert D, Harvey E, Silverman ED. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. J Pediatr. 2008;152(4):550-6.
28. Gulay CB, Dans LF. Clinical presentations and outcomes of Filipino juvenile systemic lupus erythematosus. Pediatr Rheumatol Online J. 2011;9:7.
29. Gomes RC, Silva MF, Kozu K, Bonfá E, Pereira RM, Terreri MT, et al. Features of 847 Childhood-Onset Systemic Lupus Erythematosus Patients in Three Age Groups at Diagnosis: A Brazilian Multicenter Study. Arthritis Care Res (Hoboken). 2016;68(11):1736-41.
30. Ilias I, Ali J, Ismail N, Rostenberghe H, Rahman A. Pediatric Systemic Lupus Erythematosus (SLE) Manifestations and Outcomes in a Tertiary Hospital. Lupus: Open Access. 2017;02.
31. Norris DG, Colón AR, Stickler GB. Systemic lupus erythematosus in children: the complex problems of diagnosis and treatment encountered in 101 such patients at the Mayo Clinic. Clin Pediatr (Phila). 1977;16(9):774-8.
32. Antolin J, Amerigo MJ, Cantabrana A, Roces A, Jimenez P. Systemic lupus erythematosus: clinical manifestations and immunological parameters in 194 patients. Subgroup classification of SLE. Clin Rheumatol. 1995;14(6):678-85.
33. Glidden RS, Mantzouranis EC, Borel Y. Systemic lupus erythematosus in childhood: clinical manifestations and improved survival in fifty-five patients. Clin Immunol Immunopathol. 1983;29(2):196-210.
34. Carreño L, López-Longo FJ, Monteagudo I, Rodríguez-Mahou M, Bascones M, González CM, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. Lupus. 1999;8(4):287-92.

35. Abdwani R, Rizvi SG, El-Nour I. Childhood systemic lupus erythematosus in Sultanate of Oman: demographics and clinical analysis. Lupus. 2008;17(7):683-6.
36. Cabral M, Escobar C, Conde M, Ramos M, Melo Gomes JA. Juvenile systemic lupus erythematosus in Portugal: clinical and immunological patterns of disease expression in a cohort of 56 patients. Acta Reumatol Port. 2013;38(4):274-85.
37. Caeiro F, Michielson F, Bernstein R, Hughes G, Ansell B. Systemic lupus erythematosus in childhood. Annals of the rheumatic diseases. 1981;40(4):325-31.
38. Levy DM, Peschken CA, Tucker LB, Chédeville G, Huber AM, Pope JE, et al. Influence of ethnicity on childhood-onset systemic lupus erythematosus: results from a multiethnic multicenter Canadian cohort. Arthritis Care Res (Hoboken). 2013;65(1):152-60.
39. Choi JH, Park DJ, Kang JH, Yim YR, Lee KE, Lee JW, et al. Comparison of clinical and serological differences among juvenile-, adult-, and late-onset systemic lupus erythematosus in Korean patients. Lupus. 2015;24(12):1342-9.
40. Lim SC, Chan EWL, Tang SP. Clinical features, disease activity and outcomes of Malaysian children with paediatric systemic lupus erythematosus: A cohort from a tertiary centre. Lupus. 2020;29(9):1106-14.
41. Moradinejad MH, Zamani GR, Kiani AR, Esfahani T. Clinical features of juvenile lupus erythematosus in Iranian children. Acta Reumatol Port. 2008;33(1):63-7.
42. Al Rasbi A, Abdalla E, Sultan R, Abdullah N, Al Kaabi J, Al-Zakwani I, et al. Spectrum of systemic lupus erythematosus in Oman: from childhood to adulthood. Rheumatol Int. 2018;38(9):1691-8.
43. Supavekin S, Chatchomchuan W, Pattaragarn A, Suntornpoch V, Sumboonnanonda A. Pediatric systemic lupus erythematosus in Siriraj Hospital. J Med Assoc Thai. 2005;88 Suppl 8:S115-23.
44. Chiewchengchol D, Murphy R, Morgan T, Edwards SW, Leone V, Friswell M, et al. Mucocutaneous manifestations in a UK national cohort of juvenile-onset systemic lupus erythematosus patients. Rheumatology (Oxford). 2014;53(8):1504-12.
45. Aggarwal A, Phatak S, Srivastava P, Lawrence A, Agarwal V, Misra R. Outcomes in juvenile onset lupus: single center cohort from a developing country. Lupus. 2018;27(11):1867-75.
46. Mohamed DF, Aziz ABE-DA, Hassan SA-M, Shedid NH, El-Owaidy RH, Teama MAEM. Juvenile lupus: Different clinical and serological presentations compared to adult lupus in Egypt. The Egyptian Rheumatologist. 2018;40(1):55-8.
47. Rood MJ, ten Cate R, van Suijlekom-Smit LW, den Ouden EJ, Ouwerkerk FE, Breedveld FC, et al. Childhood-onset Systemic Lupus Erythematosus: clinical presentation and prognosis in 31 patients. Scand J Rheumatol. 1999;28(4):222-6.
48. Alsaeid K, Kamal H, Haider MZ, Al-Enezi HM, Malaviya AN. Systemic lupus erythematosus in Kuwaiti children: organ system involvement and serological findings. Lupus. 2004;13(8):613-7.
49. Kumar S, Nair S, Rajam L. Case series of pediatric systemic lupus erythematosus from Kerala: comparison with other Indian series. Int J Rheum Dis. 2010;13(4):391-5.
50. Al-Mayouf S, Abdwani R, Al-Brawi S. Familial juvenile systemic lupus erythematosus in Arab children. Rheumatol Int. 2012;32(7):1939-43.
51. Watson L, Leone V, Pilkington C, Tullus K, Rangaraj S, McDonagh JE, et al. Disease activity, severity, and damage in the UK Juvenile-Onset Systemic Lupus Erythematosus Cohort. Arthritis Rheum. 2012;64(7):2356-65.
52. Fatemi A, Matinfar M, Smiley A. Childhood versus adult-onset systemic lupus erythematosus: long-term outcome and predictors of mortality. Clin Rheumatol. 2017;36(2):343-50.
53. Proceedings of the 26th European Paediatric Rheumatology Congress: part 1: Virtual. 23 - 26 September 2020. Pediatr Rheumatol Online J. 2020;18(Suppl 2):83.

54. Hoffman IE, Lauwerys BR, De Keyser F, Huizinga TW, Isenberg D, Cebecauer L, et al. Juvenile-onset systemic lupus erythematosus: different clinical and serological pattern than adult-onset systemic lupus erythematosus. Ann Rheum Dis. 2009;68(3):412-5.
55. Ramírez Gómez LA, Uribe Uribe O, Osio Uribe O, Grisales Romero H, Cardiel MH, Wojdyla D, et al. Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. Lupus. 2008;17(6):596-604.
56. Salah S, Lotfy HM, Sabry SM, El Hamshary A, Taher H. Systemic lupus erythematosus in Egyptian children. Rheumatol Int. 2009;29(12):1463-8.
57. Ambrose N, Morgan TA, Galloway J, Ionnoau Y, Beresford MW, Isenberg DA. Differences in disease phenotype and severity in SLE across age groups. Lupus. 2016;25(14):1542-50.
58. Torrente-Segarra V, Salman Monte TC, Rúa-Figueroa I, Sánchez-Alonso F, López-Longo FJ, Galindo-Izquierdo M, et al. Juvenile- and adult-onset systemic lupus erythematosus: a comparative study in a large cohort from the Spanish Society of Rheumatology Lupus Registry (RELESSER). Clin Exp Rheumatol. 2017;35(6):1047-55.
59. Fonseca R, Aguiar F, Rodrigues M, Brito I. Clinical phenotype and outcome in lupus according to age: a comparison between juvenile and adult onset. Reumatol Clin (Engl Ed). 2018;14(3):160-3.
60. Sahin S, Adrovic A, Barut K, Canpolat N, Ozluk Y, Kilicaslan I, et al. Juvenile systemic lupus erythematosus in Turkey: demographic, clinical and laboratory features with disease activity and outcome. Lupus. 2018;27(3):514-9.
61. El-Garf K, El-Garf A, Gheith R, Badran S, Salah S, Marzouk H, et al. A comparative study between the disease characteristics in adult-onset and childhood-onset systemic lupus erythematosus in Egyptian patients attending a large university hospital. Lupus. 2021;30(2):211-8.
62. Baştuğ F. Juvenile Lupus Erythematosus: Fourteen Years of Experience. Turkish Journal of Rheumatology. 2011;26:308-15.
63. Al-Mosawi Z, Al-Hermi BE, Al-Saad KK, Farid EM, Makki HA. Juvenile systemic lupus erythematosus in Bahrain. A tertiary referral center experience. Saudi Med J. 2009;30(5):667-72.
64. Amer H. Clinical Presentation of Pediatric SLE at Outpatient Clinic. MOJ Orthopedics & Rheumatology. 2015;2.
65. Tarr T, Dérfalvi B, Győri N, Szántó A, Siminszky Z, Malik A, et al. Similarities and differences between pediatric and adult patients with systemic lupus erythematosus. Lupus. 2015;24(8):796-803.
66. Artim-Esen B, Şahin S, Çene E, Şahinkaya Y, Barut K, Adrovic A, et al. Comparison of Disease Characteristics, Organ Damage, and Survival in Patients with Juvenile-onset and Adult-onset Systemic Lupus Erythematosus in a Combined Cohort from 2 Tertiary Centers in Turkey. J Rheumatol. 2017;44(5):619-25.
67. Shakeel S, Ali SR, Karim F, Ishaq S, Qaiser I, Nayani K, et al. Childhood-Onset Systemic Lupus Erythematosus: A Cohort Study. J Coll Physicians Surg Pak. 2018;28(5):365-9.
68. Kim H, Levy DM, Silverman ED, Hitchon C, Bernatsky S, Pineau C, et al. A comparison between childhood and adult onset systemic lupus erythematosus adjusted for ethnicity from the 1000 Canadian Faces of Lupus Cohort. Rheumatology (Oxford). 2019.
69. El Hadidi KT, Medhat BM, Abdel Baki NM, Abdel Kafy H, Abdelrahaman W, Yousri AY, et al. Characteristics of systemic lupus erythematosus in a sample of the Egyptian population: a retrospective cohort of 1109 patients from a single center. Lupus. 2018;27(6):1030-8.
70. Yurdakul S, Özdogan H, Hamuryudan V, Moral F, Mat C, üzün Y, et al. C 30 Behçet's syndrome in childhood. A report of 44 patients. La Revue de medecine interne. 1993;14(SUPPL. 1).
71. Kim DK, Chang SN, Bang D, Lee ES, Lee S. Clinical analysis of 40 cases of childhood-onset Behçet's disease. Pediatr Dermatol. 1994;11(2):95-101.
72. Sarica R, Azizlerli G, Köse A, Dişçi R, Ovül C, Kural Z. Juvenile Behçet's disease among 1784 Turkish Behçet's patients. Int J Dermatol. 1996;35(2):109-11.

73. Fujikawa S, Suemitsu T. Behçet disease in children: a nationwide retrospective survey in Japan. Acta Paediatr Jpn. 1997;39(2):285-9.
74. Eldem B, Onur C, Ozen S. Clinical features of pediatric Behçet's disease. J Pediatr Ophthalmol Strabismus. 1998;35(3):159-61.
75. Koné-Paut I, Yurdakul S, Bahabri SA, Shafae N, Ozen S, Ozdogan H, et al. Clinical features of Behçet's disease in children: an international collaborative study of 86 cases. J Pediatr. 1998;132(4):721-5.
76. Treudler R, Orfanos CE, Zouboulis CC. Twenty-eight cases of juvenile-onset Adamantiades-Behçet disease in Germany. Dermatology. 1999;199(1):15-9.
77. Koné-Paut I, Gorchakoff-Molinas A, Weschler B, Touitou I. Paediatric Behçet's disease in France. Annals of the rheumatic diseases. 2002;61(7):655-6.
78. Karincaoglu Y, Borlu M, Toker SC, Akman A, Onder M, Gunasti S, et al. Demographic and clinical properties of juvenile-onset Behçet's disease: A controlled multicenter study. J Am Acad Dermatol. 2008;58(4):579-84.
79. Sungur GK, Hazirolan D, Yalvac I, Ozer PA, Yuksel D, Vural ET, et al. Clinical and demographic evaluation of Behçet disease among different paediatric age groups. Br J Ophthalmol. 2009;93(1):83-7.
80. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Nadji A, Akhlaghi M, et al. Behcet's disease in Iran: analysis of 6500 cases. Int J Rheum Dis. 2010;13(4):367-73.
81. Atmaca L, Boyvat A, Yalçındağ FN, Atmaca-Sonmez P, Gurler A. Behçet disease in children. Ocul Immunol Inflamm. 2011;19(2):103-7.
82. Koné-Paut I, Darce-Bello M, Shahram F, Gattorno M, Cimaz R, Ozen S, et al. Registries in rheumatological and musculoskeletal conditions. Paediatric Behçet's disease: an international cohort study of 110 patients. One-year follow-up data. Rheumatology (Oxford). 2011;50(1):184-8.
83. Hung CH, Lee JH, Chen ST, Yang YH, Lin YT, Wang LC, et al. Young children with Behçet disease have more intestinal involvement. J Pediatr Gastroenterol Nutr. 2013;57(2):225-9.
84. Koné-Paut I, Shahram F, Darce-Bello M, Cantarini L, Cimaz R, Gattorno M, et al. Consensus classification criteria for paediatric Behçet's disease from a prospective observational cohort: PEDBD. Ann Rheum Dis. 2016;75(6):958-64.
85. Nanthapisal S, Klein NJ, Ambrose N, Eleftheriou D, Brogan PA. Paediatric Behçet's disease: a UK tertiary centre experience. Clin Rheumatol. 2016;35(10):2509-16.
86. Gallizzi R, Pidone C, Cantarini L, Finetti M, Cattalini M, Filocamo G, et al. A national cohort study on pediatric Behçet's disease: cross-sectional data from an Italian registry. Pediatr Rheumatol Online J. 2017;15(1):84.
87. Çirkinoğlu MS, Demir S, Bilginer Y, Özen S. Behçet's disease in children: single-center experience. Turk Pediatri Ars. 2019;54(3):179-84.
88. Davatchi F, Shahram F, Chams-Davatchi C, Shams H, Abdolahi BS, Nadji A, et al. Behcet's disease in Iran: Analysis of 7641 cases. Mod Rheumatol. 2019;29(6):1023-30.
89. Hu Y-C, Yang Y-H, Lin Y-T, Wang L-C, Yu H-H, Lee J-H, et al. Clinical manifestations and anti-TNF alpha therapy of juvenile Behçet’s disease in Taiwan. BMC Pediatrics. 2019;19(1):232.
90. Makmur EL, Myers SH, Hanns L, Haskard DO, Brogan P, Ambrose N. Comparing the clinical profile of adults and children with Behçet's syndrome in the UK. Clin Exp Rheumatol. 2019;37 Suppl 121(6):48-51.
91. Balbaba M, Ulaş F, Postacı SA, Çeliker Ü, Gürgöze MK. Clinical and Demographic Features of Pediatric-Onset Behçet's Disease and Evaluation of Optical Coherence Tomography Findings. Ocul Immunol Inflamm. 2020;28(4):606-12.
92. Gezgin Yıldırım D, Bakkaloğlu SA, Hasanreisoglu M, Buyan N. Disease activity and outcomes in juvenile Behçet's disease: 10 years' experience of a single centre. Clin Exp Rheumatol. 2020;38 Suppl 127(5):105-11.

93. Patterson M, Castiglioni L, Sampson L. Chronic ulcerative colitis beginning in children and teenagers. A review of 43 patients. Am J Dig Dis. 1971;16(4):289-97.
94. Postuma R, Moroz SP. Pediatric Crohn's disease. J Pediatr Surg. 1985;20(5):478-82.
95. Seo JK, Yeon KM, Chi JG. Inflammatory bowel disease in children--clinical, endoscopic, radiologic and histopathologic investigation. J Korean Med Sci. 1992;7(3):221-35.
96. Kugathasan S, Judd RH, Hoffmann RG, Heikenen J, Telega G, Khan F, et al. Epidemiologic and clinical characteristics of children with newly diagnosed inflammatory bowel disease in Wisconsin: a statewide population-based study. J Pediatr. 2003;143(4):525-31.
97. Harty S, Fleming P, Rowland M, Crushell E, McDermott M, Drumm B, et al. A prospective study of the oral manifestations of Crohn's disease. Clin Gastroenterol Hepatol. 2005;3(9):886-91.
98. Gupta N, Bostrom AG, Kirschner BS, Ferry GD, Winter HS, Baldassano RN, et al. Gender differences in presentation and course of disease in pediatric patients with Crohn disease. Pediatrics. 2007;120(6):e1418-25.
99. Gupta N, Bostrom AG, Kirschner BS, Cohen SA, Abramson O, Ferry GD, et al. Presentation and disease course in early- compared to later-onset pediatric Crohn's disease. Am J Gastroenterol. 2008;103(8):2092-8.
100. Jose FA, Garnett EA, Vittinghoff E, Ferry GD, Winter HS, Baldassano RN, et al. Development of extraintestinal manifestations in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(1):63-8.
101. Dotson JL, Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr. 2010;51(2):140-5.
102. Guariso G, Gasparetto M, Visonà Dalla Pozza L, D'Incà R, Zancan L, Sturniolo G, et al. Inflammatory bowel disease developing in paediatric and adult age. J Pediatr Gastroenterol Nutr. 2010;51(6):698-707.
103. Pytrus T, Iwańczak B, Krzesiek E, Iwańczak F. Mucocutaneous manifestations and complications in children with inflammatory bowel diseases. Pediatria Wspolczesna. 2011;13:86-91.
104. Howell JL, Bussell RM, Hegarty AM, Zaitoun H. Service evaluation of patients with orofacial granulomatosis and patients with oral Crohn's disease attending a paediatric oral medicine clinic. Eur Arch Paediatr Dent. 2012;13(4):191-6.
105. Chu HP, Logarajah V, Tan N, Phua KB. Paediatric inflammatory bowel disease in a multiracial Asian country. Singapore Med J. 2013;54(4):201-5.
106. Malaty HM, Abraham BP, Mehta S, Garnett EA, Ferry GD. The natural history of ulcerative colitis in a pediatric population: a follow-up population-based cohort study. Clin Exp Gastroenterol. 2013;6:77-83.
107. Wang XQ, Zhang Y, Xu CD, Jiang LR, Huang Y, Du HM, et al. Inflammatory bowel disease in Chinese children: a multicenter analysis over a decade from Shanghai. Inflamm Bowel Dis. 2013;19(2):423-8.
108. Wu DZ, Chen CD, Wu SC, Dai LN, Xia LG, Chen XM. A Retrospective Study on Clinical Characteristics of Paediatric Crohn's Disease. Hong Kong Journal of Paediatrics. 2014;19:169-74.
109. Ashton JJ, Coelho T, Ennis S, Batra A, Afzal NA, Beattie RM. Presenting phenotype of paediatric inflammatory bowel disease in Wessex, Southern England 2010-2013. Acta Paediatr. 2015;104(8):831-7.
110. Zhou Y, Huang Y. Inflammatory bowel disease in Chinese children: A retrospective analysis of 49 cases. Exp Ther Med. 2016;12(5):3363-8.
111. Greuter T, Bertoldo F, Rechner R, Straumann A, Biedermann L, Zeitz J, et al. Extraintestinal Manifestations of Pediatric Inflammatory Bowel Disease: Prevalence, Presentation, and Anti-TNF Treatment. J Pediatr Gastroenterol Nutr. 2017;65(2):200-6.

112. Ye Z, Zhou Y, Huang Y, Wang Y, Lu J, Tang Z, et al. Phenotype and Management of Infantile-onset Inflammatory Bowel Disease: Experience from a Tertiary Care Center in China. Inflammatory Bowel Diseases. 2017;23(12):2154-64.
113. Herzog D, Fournier N, Buehr P, Rueger V, Koller R, Heyland K, et al. Age at disease onset of inflammatory bowel disease is associated with later extraintestinal manifestations and complications. Eur J Gastroenterol Hepatol. 2018;30(6):598-607.
114. Zheng C, Huang Y, Hu W, Shi J, Ye Z, Qian X, et al. Phenotypic Characterization of Very Early-Onset Inflammatory Bowel Disease with Interleukin-10 Signaling Deficiency: Based on a Large Cohort Study. Inflamm Bowel Dis. 2019;25(4):756-66.
115. Cohen S, Padlipsky J, Yerushalmy-Feler A. Risk factors associated with extraintestinal manifestations in children with inflammatory bowel disease. European Journal of Clinical Nutrition. 2020;74(5):691-7.
116. Rawashdeh MO, Khalil B, Raweily E. Celiac disease in Arabs. J Pediatr Gastroenterol Nutr. 1996;23(4):415-8.
117. Bucci P, Carile F, Sangianantoni A, D'Angiò F, Santarelli A, Lo Muzio L. Oral aphthous ulcers and dental enamel defects in children with coeliac disease. Acta Paediatr. 2006;95(2):203-7.
118. Campisi G, Di Liberto C, Carroccio A, Compilato D, Iacono G, Procaccini M, et al. Coeliac disease: oral ulcer prevalence, assessment of risk and association with gluten-free diet in children. Dig Liver Dis. 2008;40(2):104-7.
119. Kuloğlu Z, Kirsaçlioğlu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 children. Yonsei Med J. 2009;50(5):617-23.
120. Sezgin Bolgül B, Arslanoğlu Z, Tumen EC, Yavuz I, Celenk S, Atakul F. Significance of Oral Symptoms in Early Diagnosis and Treatment of Celiac Disease. Turkiye Klinikleri Journal of Medical Sciences. 2009;29:599-604.
121. Acar S, Yetkıner AA, Ersın N, Oncag O, Aydogdu S, Arıkan C. Oral findings and salivary parameters in children with celiac disease: a preliminary study. Med Princ Pract. 2012;21(2):129-33.
122. Tosun MS, Ertekin V, M.A S, Selimoğlu M, M K, N K. Oral findings in children with celiac disease. Turkish Journal of Medical Sciences. 2012;42:613–7.
123. Bhattacharya M, Kapoor S, Dubey AP. Celiac disease presentation in a tertiary referral centre in India: current scenario. Indian J Gastroenterol. 2013;32(2):98-102.
124. Bramanti E, Cicciù M, Matacena G, Costa S, Magazzù G. Clinical Evaluation of Specific Oral Manifestations in Pediatric Patients with Ascertained versus Potential Coeliac Disease: A Cross-Sectional Study. Gastroenterol Res Pract. 2014;2014:934159.
125. Cantekin K, Arslan D, Delikan E. Presence and distribution of dental enamel defects, recurrent aphthous lesions and dental caries in children with celiac disease. Pak J Med Sci. 2015;31(3):606-9.
126. de Carvalho FK, de Queiroz AM, Bezerra da Silva RA, Sawamura R, Bachmann L, Bezerra da Silva LA, et al. Oral aspects in celiac disease children: clinical and dental enamel chemical evaluation. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;119(6):636-43.
127. Dane A, Gürbüz T. Clinical evaluation of specific oral and salivary findings of coeliac disease in eastern Turkish paediatric patients. Eur J Paediatr Dent. 2016;17(1):53-6.
128. Saraceno R, Perugia C, Ventura A, Lorè B, Chimenti S, Docimo R. Aphthous, celiac disease and other dental disorders in childhood. G Ital Dermatol Venereol. 2016;151(3):239-43.
129. Jericho H, Sansotta N, Guandalini S. Extraintestinal Manifestations of Celiac Disease: Effectiveness of the Gluten-Free Diet. J Pediatr Gastroenterol Nutr. 2017;65(1):75-9.
130. Van Kalleveen MW, de Meij T, Plötz FB. Clinical spectrum of paediatric coeliac disease: a 10-year single-centre experience. Eur J Pediatr. 2018;177(4):593-602.

131. Nurminen S, Kivelä L, Huhtala H, Kaukinen K, Kurppa K. Extraintestinal manifestations were common in children with coeliac disease and were more prevalent in patients with more severe clinical and histological presentation. Acta Paediatr. 2019;108(4):681-7.
132. Dehbozorgi M, Honar N, Ekramzadeh M, Saki F. Clinical manifestations and associated disorders in children with celiac disease in southern Iran. BMC Pediatrics. 2020;20(1):256.
133. Yılmaz S, Tuna Kirsaçlioğlu C, Şaylı T. Celiac disease and hematological abnormalities in children with recurrent aphthous stomatitis. Pediatrics International. 2020;62.
134. Niknam R, Salehi A, Molavi Vardanjani H, Fattahi MR, Dehghani SM, Honar N, et al. Different Clinical Features of Celiac Disease in Children, Adolescents, and Adults; a Cross-sectional Study. Middle East J Dig Dis. 2021;13(2):121-30.
135. Richa, Sharma S, Sharma B. Original Article The Presentation Pattern of Celiac Disease in Central India - A Prospective Study in Children. Journal of Nepal Paediatric Society. 2021;40:255.
136. Villemur Moreau L, Dicky O, Mas E, Noirrit E, Marty M, Vaysse F, et al. Oral manifestations of celiac disease in French children. Arch Pediatr. 2021;28(2):105-10.
137. GÜNGÖRER V, YORULMAZ A, ARSLAN Ş. Evaluation of Clinical and Laboratory Characteristics of Patients with PFAPA Syndrome. Güncel Pediatri.18(3):444-56.
138. Padeh S, Brezniak N, Zemer D, Pras E, Livneh A, Langevitz P, et al. Periodic fever, aphthous stomatitis, pharyngitis, and adenopathy syndrome: clinical characteristics and outcome. J Pediatr. 1999;135(1):98-101.
139. Thomas KT, Feder HM, Jr., Lawton AR, Edwards KM. Periodic fever syndrome in children. J Pediatr. 1999;135(1):15-21.
140. Tasher D, Somekh E, Dalal I. PFAPA syndrome: new clinical aspects disclosed. Arch Dis Child. 2006;91(12):981-4.
141. Garavello W, Romagnoli M, Gaini RM. Effectiveness of adenotonsillectomy in PFAPA syndrome: a randomized study. J Pediatr. 2009;155(2):250-3.
142. Feder HM, Salazar JC. A clinical review of 105 patients with PFAPA (a periodic fever syndrome). Acta Paediatr. 2010;99(2):178-84.
143. Król P, Böhm M, Sula V, Dytrych P, Katra R, Nemcová D, et al. PFAPA syndrome: clinical characteristics and treatment outcomes in a large single-centre cohort. Clin Exp Rheumatol. 2013;31(6):980-7.
144. Hofer M, Pillet P, Cochard MM, Berg S, Krol P, Kone-Paut I, et al. International periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis syndrome cohort: description of distinct phenotypes in 301 patients. Rheumatology (Oxford). 2014;53(6):1125-9.
145. Perko D, Debeljak M, Toplak N, Avčin T. Clinical features and genetic background of the periodic Fever syndrome with aphthous stomatitis, pharyngitis, and adenitis: a single center longitudinal study of 81 patients. Mediators Inflamm. 2015;2015:293417.
146. Mehregan FF, Ziaee V, Ahmadinejad Z, Tahghighi F, Sabouni F, Moradinejad MH. Periodic Fever, Aphthous Stomatitis, Pharyngitis and Cervical Adenitis (PFAPA) Syndrome in Iranian Children First Report of Iranian Periodic Fever and Autoinflammatory Registry (IPFAIR). Iran J Pediatr. 2014;24(5):598-602.
147. Batu ED, Kara Eroğlu F, Tsoukas P, Hausmann JS, Bilginer Y, Kenna MA, et al. Periodic Fever, Aphthosis, Pharyngitis, and Adenitis Syndrome: Analysis of Patients From Two Geographic Areas. Arthritis Care Res (Hoboken). 2016;68(12):1859-65.
148. Rigante D, Vitale A, Natale MF, Lopalco G, Andreozzi L, Frediani B, et al. A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. Clin Rheumatol. 2017;36(2):463-8.
149. Costagliola G, Maiorino G, Consolini R. Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome (PFAPA): A Clinical Challenge for Primary Care Physicians and Rheumatologists. Front Pediatr. 2019;7:277.

150. Ibáñez Alcalde MLM, Caldevilla Asenjo L, Calvo Rey C, García-Mon Marañés F, Blázquez Gamero D, Saavedra Lozano J, et al. Characteristics and Disease Course in a Cohort of Children With PFAPA Syndrome in the Community of Madrid, Spain. Reumatol Clin (Engl Ed). 2019;15(6):355-9.
151. Takeuchi Y, Shigemura T, Kobayashi N, Nagumo H, Furumoto M, Ogasawara K, et al. Clinical features and new diagnostic criteria for the syndrome of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis. Int J Rheum Dis. 2019;22(8):1489-97.
152. Sicignano LL, Rigante D, Moccaldi B, Massaro MG, Delli Noci S, Patisso I, et al. Children and Adults with PFAPA Syndrome: Similarities and Divergences in a Real-Life Clinical Setting. Adv Ther. 2021;38(2):1078-93.
153. Pehlivan E, Adrovic A, Sahin S, Barut K, Kul Cınar O, Kasapcopur O. PFAPA Syndrome in a Population with Endemic Familial Mediterranean Fever. J Pediatr. 2018;192:253-5.
154. Butbul Aviel Y, Harel L, Abu Rumi M, Brik R, Hezkelo N, Ohana O, et al. Familial Mediterranean Fever Is Commonly Diagnosed in Children in Israel with Periodic Fever Aphthous Stomatitis, Pharyngitis, and Adenitis Syndrome. J Pediatr. 2019;204:270-4.
155. Hentgen V, Grateau G, Stankovic-Stojanovic K, Amselem S, Jéru I. Familial Mediterranean fever in heterozygotes: are we able to accurately diagnose the disease in very young children? Arthritis Rheum. 2013;65(6):1654-62.
156. Behjati S, Zilbauer M, Heuschkel R, Phillips A, Salvestrini C, Torrente F, et al. Defining eosinophilic colitis in children: insights from a retrospective case series. J Pediatr Gastroenterol Nutr. 2009;49(2):208-15.
157. Gaggiano C, Vitale A, Obici L, Merlini G, Soriano A, Viapiana O, et al. Clinical Features at Onset and Genetic Characterization of Pediatric and Adult Patients with TNF-α Receptor-Associated Periodic Syndrome (TRAPS): A Series of 80 Cases from the AIDA Network. Mediators Inflamm. 2020;2020:8562485.
158. Chan LG, Parashar UD, Lye MS, Ong FG, Zaki SR, Alexander JP, et al. Deaths of children during an outbreak of hand, foot, and mouth disease in sarawak, malaysia: clinical and pathological characteristics of the disease. For the Outbreak Study Group. Clin Infect Dis. 2000;31(3):678-83.
159. Janis IL. Groupthink. IEEE Engineering Management Review. 2008;36(1):36.
160. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International Journal of Epidemiology. 2019;48(6):1740-g.
161. Agency MHpR. Safeguarding patient data CPRD webpage: National Institute for Health and Care Research 2022 [Available from: https://cprd.com/safeguarding-patient-data.
162. Team RC. R: A language and environment for statistical

computing. R Foundation for Statistical Computing, Vienna, Austria; 2013.
163. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Van Staa T, et al. Data resource profile: clinical practice research datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.
164. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. Rheumatology. 2017;56(11):1945-61.
165. Alatab S, Sepanlou SG, Ikuta K, Vahedi H, Bisignano C, Safiri S, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet gastroenterology & hepatology. 2020;5(1):17-30.
166. Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999–2012. Annals of the Rheumatic Diseases. 2016;75(1):136.

167. Calamia KT, Wilson FC, Icen M, Crowson CS, Gabriel SE, Kremers HM. Epidemiology and clinical characteristics of Behçet's disease in the US: a population-based study. Arthritis and rheumatism. 2009;61(5):600-4.
168. Freeman K, Ryan R, Parsons N, Taylor-Phillips S, Willis BH, Clarke A. The incidence and prevalence of inflammatory bowel disease in UK primary care: a retrospective cohort study of the IQVIA Medical Research Database. BMC Gastroenterology. 2021;21(1):139.
169. Shulman JD. Prevalence of oral mucosal lesions in children and youths in the USA. Int J Paediatr Dent. 2005;15(2):89-97.
170. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6(9):538-46.
171. Michaell A. Huber D. Assessment of Oral Ulceration. BMJ Best Practice online: BMJ; 2018 22 June 2018.

Appendix A

Example of spreadsheet used to collect data from included manuscripts

Study title	Date published	Author(s)	Country	Summary of content	Level of evidence	Definition of disease	Time point of symptom recording	Condition	Number of patients	Age (1st symptom)	Female (%)	Ethnicity

Continued…

Mean and/ or median age at diagnosis (range) (yrs)	Mean and/ or median age at onset (range) (yrs)	Mouth ulcer frequency (%)	Symptoms added in a new column as they appear in manuscript (%)	

Appendix B

Example of PPIE phase two survey for patients/ parents with experience of SLE

Thank you for taking the time to view this questionnaire. We are a research team based at Alder Hey Children's NHS Trust in association with the University of Liverpool. We are currently conducting a study into the risk of developing SLE (and other conditions) in children who go to their GP with mouth ulcers.

Participant information sheet

Invitation

This is an opportunity to share your thoughts on some aspects of this study about childhood SLE, via a short questionnaire.

What is the purpose of this questionnaire?

Your responses will help shape this study so that we can provide meaningful results and share these in a way that benefits patients and their families in the future, who may be having similar experiences to you. As you and other participants share your views with us, we are able to get a better of understanding of how research can be tailored to the exact people it is hoping to help.

Criteria for participation

We are looking for responses from people who experienced SLE symptoms at less than 18yrs old, or their parents/guardians.

What does participation involve?

Participation is voluntary. It will involve answering 9 questions. Questions 1-3 will ask some background information about your experience of childhood SLE. Questions 4-9 will ask about the research study we are conducting and your opinions on it. It should take less than 10 mins to answer all of the questions.

Confidentiality

All responses will be kept confidential and anonymised. The anonymised responses will be presented in the thesis manuscript, written publication and patient information leaflet that will be created for this study. By participating in this questionnaire, you agree to this.

Data handling

A password protected laptop will be used to access and analyse the responses to this questionnaire. All of the collected data will be kept securely on the laptop for the duration of the study.

Who has reviewed this questionnaire?

The supervisors of this study, the team at Lupus UK and a kind patient volunteer from Lupus UK have reviewed and approved this questionnaire.

If you are happy with the above, please continue to the first question.

1. Are you...?

A person with SLE

The parent/guardian of a person with SLE (please answer the remaining questions on behalf of your child)

2. At what age did you (/ your child) first experience symptoms of SLE?

Less than 18 yrs old

More than 18 yrs old (this questionnaire is looking for responses from people/parents who have experienced childhood SLE, we do not require you to answer any further questions, thank you.)

Not sure

3. Have you (/ has your child) ever experienced mouth ulcers as a symptom of SLE?

Yes

No

Not sure

4. Thinking back to before you were (/ your child was) diagnosed and SLE was first mentioned to you (if there was no uncertainty before your (/their) diagnosis you may wish to answer N/A).

What information would have been helpful to you and your family at this stage? (Choose as many options as apply)

- How to treat the symptoms you were (/your child was) experiencing
- The risk of a diagnosis (e.g. SLE) given your (/your child's) symptoms and other factors (age/sex/ ethnicity etc.)
- Signposting to sources of correct information about SLE
- An explanation as to why you were (/your child was) experiencing these symptoms
- Information about support groups and helplines for people (/parents of children) with SLE
- A description of the timeline to expect (e.g. time to diagnosis, what appointments might look like after diagnosis, prognosis etc.)
- 'Red flag' information (i.e. what symptoms should prompt a visit to A&E/ further contact with the GP)
- Other (please specify)

- N/A

5. The main outcome of this study is to be able to calculate a risk number (eg. 1 in 100 children) to tell people the likelihood of a systemic disease diagnosis (such as SLE) in children who go to their GP with mouth ulcers.

For example: 'Given that you have mouth ulcers, your risk of being diagnosed with SLE in the next 2yrs is...'

Do you think this is a good or a bad outcome?

- Extremely bad
- Somewhat bad
- Neither good nor bad
- Somewhat good
- Extremely good

6. Please explain your answer to the previous question.

Why do you think a 'risk number' is a good/bad outcome?

7. Can you think of any additional outcomes you would like to see in this study?

eg. What else would you have liked to know about diagnosis/ prognosis in those very early stages (when you/your child experienced first symptoms/ when you were going to your first appointments with specialists)?

8. *Think about a healthcare professional saying the following sentence to you and your family before diagnosis...*

'In the next year, your X of an SLE diagnosis is 1 in 100.'

Drag and drop the following words into order based on which you would have preferred in the above sentence. (Put your favourite first and your least favourite last)

Please add text next to any words you feel strongly about to explain why.

X= Risk

X= Chance

X= Probability

X= Likelihood

X= Susceptibility (to)

9. Most 'children' diagnosed with SLE are between the ages of 14-18 with many people only receiving a full diagnosis in their 20s, hence we don't believe 'children' is the correct term to refer to our childhood SLE patients.

How do you think we should refer to childhood SLE patients in this study?

Drag and drop these words from most to least favourite (please add a comment next to any words you feel strongly about).

Feel free to add your own word and put it into your rankings, if not just leave 'Other' at the bottom.

Young people

Adolescents

Teenagers/ Teens

Young adults

Children

Other

If you have any additional comments about this study please leave them below.

Appendix C

Protocol for access to CPRD data

INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

PART 1: APPLICATION FORM

IMPORTANT

Both parts of this application must be completed in accordance with the guidance note 'Completion of the ISAC Protocol Application Form', which can be found on the CPRD website (https://cprd.com/research-applications).

FOR ISAC USE ONLY	
Protocol No. -	**Submission date -**

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. **Study Title (Max. 255 characters including spaces)**

Assessing the risk of systemic diseases, such as Behcet's, SLE and IBD, in children that present to primary care with mouth ulcers.

2. Research Area (place 'X' in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	X	Methodological	
Health Services Delivery			

3. Chief Investigator

Title:	Professor
Full name:	Michael W. Beresford
Job title:	Brough Chair and Professor of Child Health, Honorary Consultant Paediatric Rheumatologist
Affiliation/organisation:	Institute of Translational Medicine, University of Liverpool / Alder Hey Children's NHS Foundation Trust
Email address:	M.W.Beresford@liverpool.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	N

4. Corresponding Applicant

Title:	Miss
Full name:	Natasha Goss
Job title:	MPhil student
Affiliation/organisation:	Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool
Email address:	hlngoss@liverpool.ac.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	Y

5. List of all investigators/collaborators

Title:	Dr
Full name:	Clare Pain
Job title:	Consultant Paediatric Rheumatologist
Affiliation/organisation:	Alder Hey Children's NHS Foundation Trust
Email address:	Clare.pain@alderhey.nhs.uk
CV Number (if applicable):	
Will this person be analysing the data? (Y/N)	N

Title:	Dr
Full name:	Kate Fleming
Job title:	Honorary Senior Fellow

Affiliation/organisation:	University of Liverpool
Email address:	kate.fleming@liverpool.ac.uk
CV Number (if applicable):	481_15
Will this person be analysing the data? (Y/N)	Y

6. Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name(s):
Dr Kate Fleming

List below the member(s) of the research team who have statistical expertise.

Name(s):
Dr Kate Fleming
Professor Michael W Beresford

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):
Dr Kate Fleming
Professor Michael W Beresford

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):
Miss Natasha Goss
Professor Michael W Beresford
Dr Clare Pain

ACCESS TO THE DATA

7. Sponsor of the study

Institution/Organisation:	University of Liverpool
Address:	Faculty of Health and Life Sciences, University of Liverpool Brownlow Hill, Liverpool, L69 3BX

8. Funding source for the study

Same as Sponsor?	Yes	X	No	
Institution/Organisation:	University of Liverpool			
Address:	Faculty of Health and Life Sciences, University of Liverpool Brownlow Hill, Liverpool, L69 3BX			

9. Institution conducting the research

Same as Sponsor?	Yes	X	No	
Institution/Organisation:	University of Liverpool			
Address:	Faculty of Health and Life Sciences, University of Liverpool Brownlow Hill, Liverpool, L69 3BX			

10. Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	

Institutional Multi-study Licence	X
Institution Name	University of Liverpool
Institution Address	Brownlow Hill, Liverpool, L69 3BX

Will the dataset be extracted by CPRD?

Yes		No	X

1. Data Processor(s):

Processing	X
Accessing	X
Storing	X

Processing area (UK/EEA/Worldwide)	UK
Organisation name	CSD, University of Liverpool
Organisation address	Brownlow Hill Liverpool L69 3GL

INFORMATION ON DATA

11. Primary care data (place 'X' in all boxes that apply)

CPRD GOLD		CPRD Aurum	X

12. **Please select any linked data or data products being requested7**

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data			
HES Admitted Patient Care			
HES Outpatient			
HES Accident and Emergency		NCRAS Cancer Registration Data	
HES Diagnostic Imaging Dataset		NCRAS Cancer Patient Experience Survey (CPES) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS Systemic Anti-Cancer Treatment (SACT) data	
CPRD Mother Baby Link		NCRAS National Radiotherapy Dataset	
Pregnancy Register		NCRAS Quality of Life Cancer Survivors Pilot (QOLP)	

Mental Health Data Set (MHDS)		NCRAS Quality of Life Colorectal Cancer Survivors (QOLC)	

Area Level Data (place '**X**' in <u>one</u> Practice / Patient level box that may apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (index other than the most recent)		Patient Level Index of Multiple Deprivation Domains	
Practice Level Index of Multiple Deprivation Domains		Patient Level Carstairs Index for 2011 Census	
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland)		Patient Level Townsend Score	
2011 Rural-Urban Classification at LSOA level		2011 Rural-Urban Classification at LSOA level	

13. Are you requesting linkage to a dataset not listed above?

Yes		No	**X**

14. Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes		No	**X**

VALIDATION/VERIFICATION

Does this protocol describe an observational study using purely CPRD data?

Yes	**X**	No	

Does this protocol involve requesting any additional information from GPs, or contact with patients?

Yes		No	**X**

PART 2: PROTOCOL INFORMATION

Applicants must complete all sections listed below

Applications with sections marked 'Not applicable' without justification will be returned as invalid

A. Study Title (Max. 255 characters, including spaces)

Assessing the risk of systemic diseases, such as Behcet's, SLE and IBD, in children that present to primary care with mouth ulcers: A descriptive, observational study using the Clinical Practice Research Datalink

B. Lay Summary (Max. 250 words)

Mouth ulcers are very common in children, it is hard to say exactly how common as GPs are not made aware of most episodes. Most ulcers should resolve within 3 weeks without any treatment, some may occur more than once and these are said to be recurrent. Although ulcers may cause discomfort especially if recurrent, they are generally considered harmless. However, in some cases they are a symptom or 'warning sign' of a more serious health concern.

Some of these health concerns can involve the malfunction of the body's natural defences to infections (immune-mediated). For example, Behcet's disease causes inflammation of the blood vessels; lupus causes the body's defence system to attack healthy parts of the body; and inflammatory bowel disease (IBD) causes inflammation in the gut.

Mouth ulcers can also give us clues to processes happening in the body that we cannot initially see, for example infections, allergies, cancerous changes, skin conditions or nutrients lacking in the diet. There are also some logical causes of mouth ulcers such as burns from hot food, poor hygiene in the mouth, or toothbrushing damaging skin inside the mouth.

It is understood that mouth ulcers can be a marker of ill health, however the risk of progressing from a simple mouth ulcer to a serious illness is unknown.

This study will investigate what happens to children that attend their GP with a mouth ulcer. It will investigate the risk of these children being diagnosed with certain specific immune-mediated conditions later in life.

C. Technical Summary (Max. 300 words)

There are approximately 8.89 million children under the age of 18 years in the UK. With a prevalence of 5-10%, about 0.67 million of them experience recurrent mouth ulcers. Due to variance in health seeking behaviours this is likely an underestimation, especially in terms of transient ulceration.

Evidence suggests that mouth ulcers may not only act as a symptom of certain immune-mediated conditions but can be a presenting complaint months or years before diagnosis. The specific immune-mediated conditions of interested are Behcet's disease, systemic lupus erythematous (SLE) and inflammatory bowel disease (IBD).

This study will extract data on a sample of children aged under 16 years from the Clinical Practice Research Datalink (CPRD). The database will be used to investigate: (1) the risk of systemic disease in children who present to primary care with mouth ulcers; and (2) the initial presentation characteristics, focussing on mouth ulcers, of children who have been diagnosed with a systemic disease.

Incidence and odds ratios will be calculated to determine the risk associated with mouth ulcers in relation to systemic disease. Multifactor analysis will be used to determine if these risks are associated with other factors such as sex, age, deprivation, or other presentation characteristics. Linked IMD data will be utilised to detect potential differences in outcomes between socioeconomic groups, hence informing clinical practice to reduce healthcare inequalities in the long term. The combination of 2 study designs will allow conclusions to be drawn about the incidence of systemic diseases presenting as mouth ulcers and the outcome risks associated with the presentation.

D. Outcomes to be Measured

1. Systemic diseases: Behcet's disease, SLE and/or IBD.

E. Objectives, Specific Aims and Rationale

The aim is to examine the association between the presentation of mouth ulcers in primary care and subsequent onset of systemic disease in childhood.

The research aims are:

1. To examine the incidence and prevalence of systemic disease (Behcet's, SLE or IBD) in a population presenting with mouth ulcers at age<16, coded for in the primary care setting.
2. To examine the prior coding for mouth ulcers in a population of children with a systemic disease diagnosis (Behcet's, SLE or IBD).

Rationale:

An understanding of the risk of progression to systemic disease from mouth ulcer presentation in primary care, as well as understanding how common this presentation is for the specified diseases, will aid clinicians in making informed decisions as to the best management options for their patients. The data that this study produces along with clinical expertise and current literature will ensure families can be better informed of what to expect in the future for their children with mouth ulcers.

F. Study Background

Oral ulceration is a common complaint in childhood affecting approximately 9% of all children (169). Most ulcers are benign and self-limiting, lasting less than 2 weeks, however some become recurrent with repeated episodes differentiated by intermittent healing (3). Ulcers within the oral cavity cause local pain and inflammation, this can result in the primary morbidity in the paediatric population which is dehydration due to reduced oral intake (4). Peak prevalence of recurrent ulcers is seen at ages 10-19 years although severity and frequency of multiple ulcers declines with age (4).There is essentially no mortality associated with simple, solitary ulcers unless they are a symptom of a more significant illness.

There are 3 key systemic diseases of interest related to the issue of mouth ulcers: Behcet's disease, systemic lupus erythematous (SLE) and inflammatory bowel disease (IBD). Behcet's disease is a heterogenous vasculitis which manifests as mouth and genital ulcers as well as widespread involvement of the skin, eyes, joints, central nervous and gastrointestinal systems (5). The presence of these diagnostic symptoms occurs much less in the paediatric population compared to adults, with a prevalence of 4.2 per million UK children under the age of 16yrs (6). SLE is defined as a chronic autoimmune condition that is not limited to one organ system (7). Again childhood onset is rare with a prevalence of 33-88 per million children(170). IBD can be categorised into Crohn's disease (CD) and ulcerative colitis (UC), both of which are chronic, idiopathic inflammation of the gut differentiated by which part of the system they affect (9). The overall prevalence of IBD is 770 per million children, with CD being twice as prevalent as UC(11). Although individually some of these conditions are rare, when combined together under the umbrella term of 'systemic diseases' the extent of the issue becomes much greater.

All 3 key systemic diseases listed above mention oral ulcers in their diagnostic criteria (12-14). Hence, if oral ulcers are present at the time of clinician assessment they can be used to confirm or contribute to a diagnosis. However, a previous (or resolved) presentation of oral ulceration in childhood, is not yet proven as a risk factor for any of the systemic diseases. This is partly because there are no prospective studies looking into the progression from mouth ulcer presentation in childhood to the subsequent diagnosis of a systemic disease, and hence current predictions rely on individual clinicians' experiences. If evidence could be found to confirm or deny the suspicion that oral ulceration increases children's risk of receiving a systemic disease diagnosis, as well as to assess the contribution of other risk factors and the variance with each condition, then this would directly inform clinicians in counselling patients, and hence children and their families would benefit directly.

As detailed in the BMJ Best Practice guideline entitled 'Assessment of Oral Ulceration (171) there are various other aetiologies of oral ulcers that can be divided into the following categories: inflammatory/ immune-mediated,

deficiencies, dermatological, allergic/toxic, infections, neoplastic and traumatic. Of these categories, 4 can present with oral ulcers some time before the onset of serious disease and hence allow a window of potential treatment opportunity. Firstly inflammatory/ immune-mediate conditions, including periodic fevers such as PFAPA syndrome, necrotising sialometaplasia, MAGIC syndrome, TRAPs, Reiter's/ reactive arthritis, giant cell arteritis, granulomatosis with polyangitis, chronic GVHD, and coeliac disease (171). Also certain dietary deficiencies such as iron, B12, vitamin C or folate may present like this; and dermatological conditions such as pemphigus vulgaris, mucous membrane pemphigoid, paraneoplastic pemphigus, epidermolysis bullosa acquisita and linear IgA bullous dermatosis (171). Finally, aetiologies that cannot be specifically categorised such as poor dental hygiene and idiopathic recurrent aphthous stomatitis (RAS). With the breadth of conditions that oral ulcers can be related to, it is clearly an area requiring more investigation to prevent missed treatment opportunities.

The proposed study will investigate anonymised, electronic, primary care records from the CPRD between 1990 and 2019, to contribute to the described area of missing literature. The aim of the study is to assess the association between the presentation of mouth ulcers in primary care and the diagnosis of systemic disease, using a two strand approach.

The first strand will attempt to stratify the risk, for children presenting with oral ulcers to their GP, of progressing onto a systemic disease. The second strand will take a retrospective look at how children diagnosed with Behcet's, SLE or IBD initially presented to their primary care physician. It is anticipated that the results of this study will contribute to the current understanding and hence allow clinicians more confidence in offering the right management strategies to patients and their families.

G. Study Type

Descriptive epidemiology study.

H. Study Design

We will conduct two complementary studies:

- Firstly a cohort study design will examine the incidence and prevalence of systemic disease (specifically, Behcet's disease, SLE and/or IBD) and other significant outcomes (described in 'Outcomes' section) in a paediatric population with mouth ulcers coded for in the primary care setting, compared with a population of children without mouth ulcers.
- Secondly, as outcomes of interest are rare within paediatric populations, a descriptive case-control study will examine the odds of prior coding for mouth ulcers in a population of children with a systemic disease diagnosis (Behcet's, SLE or IBD) (cases) compared with an ages and sex-matched cohort of children without systemic disease.

I. Feasibility counts

Using the June 2021 Aurum release we identified:

- 487,036 children under 16yrs with a code for mouth ulcers during the study period and with at least 2 years follow up after index.
- For outcomes (max. age at index 16yrs, during the study period:
    - Behcet's=219,
    - UC=4333,
    - Crohn's=1659,
    - SLE= 1168,
    - IBD= 2211,
    - All=8750.

J. Sample size considerations

Cohort study: With an expected incidence of systemic disease of only 0.01%, α=0.05, the proportion of patients with mouth ulcers 50%, and 80% power, we would require a sample size of 156,944 to detect an incidence rate ratio of 3.0. We estimate in the feasibility counts to have significantly more patients with available data.

Case-control study: we will match controls to cases in a ratio of 5:1 based on age and sex. With α=0.05, an expected 5% of controls exposed to mouth ulcers, power of 80%, to detect an odds ratio of 2 we would require 513 cases. We therefore may not have sufficient power to examine Behcets disease as an independent outcome. All other outcomes should have a sufficient number of cases within the dataset as described in 'Feasibility counts' section.

K. Planned use of linked data (if applicable):

Patient Level Index of Multiple Deprivation – to reflect patient socioeconomic status

Results of this study will be of direct benefit to patients in England in providing contemporaneous risks of developing systemic disease for communication to patients and their carers.

L. Definition of the Study population

- The study period will be from 1 Jan 1990 to 31 Dec 2019.
- The study will use an open design with patients entering when they are registered at a research active practice, aged between 0 and 16. Patients will exit at their transfer out date, death date, practices last collection date, or 31 Dec 2019 (whichever is earliest).

Inclusion:

- Data meeting CPRD quality standards
- Permanently registered children (</=16 years old)
- Patients for whom Patient Level Index of Multiple Deprivation is available.
- Patient records have an acceptable patient flag.

M. Selection of comparison group(s) or controls

In the cohort study, the exposed group will be children with a record of mouth ulcers (as described below in 'Outcomes, exposures and covariates' section) with a comparison group of children who do not have a prior record of mouth ulcers frequency matched at index date by age, sex and practice at a maximum ratio of 2:1.

In the case-control study, cases will be selected based on occurrence of any of the outcome measures (as defined in 'Outcomes, exposures and covariates' section). Controls will be frequency matched at index date of their cases by age, sex and general practice at a maximum ratio of 5:1 from the population who do not have the outcome(s) of interest at pseudo index date.

N. Exposures, Outcomes and Covariates

All exposures, outcomes and covariates will be defined by Read codes, translated to medcodeid (see code list at specific appendices). We base many of our codes lists on the work by Kuan et al [protocol 16_022], (https://github.com/spiros/chronological-map-phenotypes) which we have mapped to Aurum specific code lists. Where code lists were not in existence we have created these code lists, verified by clinicians on the study team.

Exposures:

GP recorded mouth ulcers: We will take first record of mouth ulcer within research ready data as date of index for the cohort study. If possible, we will exclude mouth ulcers related to infection or neoplasm, subject to accurate coding. (See appendix A)

Outcomes:

Systemic diseases**-** For both studies we will use a composite outcomes measure of any of the following systemic diseases. Where power permits we will look at each individual outcome.

- Behcet's disease (see appendix B)
- Inflammatory bowel disease (IBD) (code for Crohn's or ulcerative colitis or non-specific IBD) (see appendix C)
- Systemic lupus erythematous (SLE) (see appendix D)

Covariates:

1. Age – index date of ulcer for the cohort study, and at index date of outcome for the case control study
2. Gender – defined using the CPRD sex variable.
3. Ethnicity- defined using CPRD
4. Socio-economic status – evaluated by assessing patient-level Index of Multiple Deprivation (IMD) scores and categorising into quintiles of deprivation (1^{st} quintile = least deprived, 5^{th} quintile = most deprived)
5. Family history of systemic disease such as Behcet's, SLE or IBD.
6. A number of other conditions / presentations relating to conditions that may also present as mouth ulcers will be examined at baseline. For example:
    - Inflammatory/ immune related (chronic GVHD, Coeliac disease, giant cell arteritis, necrotising sialometaplasia, periodic fever syndromes (e.g. PFAPA), Reiter's syndrome, Granulomatosis with polyangiitis, TRAPs);
    - Deficiencies (B12, folate, iron, vitamin C);

- Dermatological (epidermolysis bullosa acquisitia, mucous membrane pemphigoid, pemphigus vulgaris);
- Others (RAS, poor dental hygiene).

O. Data/ Statistical Analysis

In both studies, statistics for all variables will be calculated and tabulated using numbers and proportions for categorical data and median, range, mean and standard deviation for continuous variables.

In the cohort study, we will use a flexible parametric survival model to estimate the risk of outcome (composite, and individual) comparing exposed and comparison unexposed populations. Comparisons will be adjusted or stratified for age at onset, sex, IMD and ethnicity. Practice will be used as a random effect within the model to account for exposure and outcome clustering at GP level. Incidence rates, incidence rate ratios and hazard ratios for outcomes will be derived from the model.

In the case control study, logistic regression will be used to model of prior mouth ulcers in the population of cases and controls, adjusting for age, sex, IMD and ethnicity.

All tests will be two-tailed, and P-value <0.05 will be considered statistically significant. Data handling and statistical analysis will be performed in R.

P. Plan for addressing confounding

Factors such as age, sex, socio-economic status (IMD) and ethnicity, that have the potential to be confounders, will be included in the logistic regression models for both studies. See 'Exposures, outcomes and covariates' and 'Data/statistical analysis' above for full description of methodology.

Q. Plans for addressing missing data

Patients will only be included if their record has an acceptability flag hence all will have age and sex information available. We accept, however, that IMD data and family history status is unlikely to be available for all patients.

Level of missingness of any variables of interest will be reported.

R. Patient or user group involvement

We will use structured, meaningful patient and public involvement and engagement (PPIE) for children and their families, using the established framework of the UK's Experimental Arthritis Treatment Centre for children (EATC4Children), based at the University of Liverpool and Alder Hey children's NHS Foundation Trust. This includes the expertise of the EATC4Children's own PPI team and patient advisors as well as the GenerationR Young Person's Advisory Group (YPAG). We will work alongside children, young people and their families to inform them of the study and get their input into it, as well as develop a child/patient/family-friendly summary of research findings and promote the study and its findings through Young Research Ambassadors.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

We will present the results of this study in an appropriate scientific peer-reviewed journal, at national (e.g. British Society of Rheumatology) and international academic meetings (e.g. Paediatric Rheumatology European Society) and at internal rheumatology academic meetings. An MPhil thesis of this study will be submitted to The University of Liverpool as part of the corresponding author's MPhil.

When distributing and sharing the findings, the CPRD policy regarding data presentation will be adhered to.

Conflict of interest statement:

No applicants or collaborators have any conflicts of interest.

T. Limitations of the study design, data sources, and analytic methods

Coding – The accuracy of GP coding will affect the quality of patient data in this study.

Disease acquisition – The date the first code appears in the patient record will be used as the date of acquisition of disease. We understand that this may not correlate with the onset of disease/ symptoms or the date of diagnosis in secondary care, especially in the rare systematic diseases. Furthermore, the diagnosis of disease can lead to more healthcare contacts and investigations hence increasing the likelihood of further diagnoses.

Primary care data – We are aware of the fact that some conditions are likely to be under reported in primary care data, particularly those that may present at first to a secondary care setting. However, due to the paediatric population we are investigating and the mild severity of the majority of mouth ulcers, we are confident that if severe enough to warrant patient/family concern, they are likely to mention this in a primary care setting, and therefore the data will be representative of the majority of patients with severe mouth ulcers, who will most likely present first within the primary care setting.

Missing IMD data – It is likely that IMD data will not be available for all patients. There is a risk of bias if patients excluded for missing data are characteristically different from those included. To counter this, we will report the baseline characteristics of both included and excluded patients including information about variables of interest. We may stratify by IMD if appropriate.

Missing family history data- If family history of systemic disease is coded for this is likely accurate. However, a high level of missingness is anticipated in GP coding. If there is not a code for family history of systemic disease this could represent either: no family history of systemic disease (i.e. the question was asked, the answer was negative and hence the code was not added); or that the question was never asked. The latter is much more likely in the control population who don't have a systemic disease themselves, hence introducing information bias. If there are high levels of missingness in one group compared with another and stratification by family history is not appropriate, this variable may have to be excluded.

Case-control study – The feasibility counts suggest that there may not be sufficient data to power the case- control studies for each individual condition of interest. We will thus use a composite outcome as our primary analysis and conduct additional analyses based on individual conditions, reporting the results with explicit caveats that the data were not sufficiently powered to detect relatively small differences in odds of mouth ulcers.

List of Appendices

Appendix D

Mouth ulcer Read code list

MedCodeId	Term	Original ReadCode	Cleansed ReadCode	SnomedCT ConceptId	SnomedCT DescriptionId
6013013	Chronic ulcerative pulpitis	J0204	J020400	2955000	6013013
21933011	Traumatic ulceration of tongue	J0901	J090100	12779007	21933011
302257010	Major aphthous ulceration	J0821	J082100	196531008	302257010
84787019	Traumatic ulcer of oral mucosa	J08z8	J08z800	50882004	84787019
254290015	O/E - ulcer on tongue	2567	2567.00	163173009	254290015
254248014	O/E - mouth ulcer	2533-1	2533.11	163145007	254248014
254249018	O/E - mouth ulcer present	2533	2533.00	163145007	254249018
499767017	Lip ulcer	J0858	J085800	64143008	499767017
301037015	Acute ulcerative tonsillitis	H032	H032.00	195668008	301037015
483164010	Mouth ulcer	J082-1	J082.11	26284000	483164010
419862014	Recurrent mouth ulcers	J0822-1	J082211	723177002	182901000006115
103631000006114	Tonsil ulcer	H14y4	H14y400	16485001	103631000006114
885661000006114	Aphthous ulcers - mouth ulcers	J082-99	J082.99	426965005	885661000006114
701831000006119	Minor aphthous ulceration	J0820	J082000	307772002	701831000006119
1786583018	Recurrent aphthous ulceration	J0822	J082200	398870000	1786583018
34685016	Gingivostomatitis	J0314	J031400	20607006	34685016
1833014	Ulcerative stomatitis	J0800	J080000	450005	1833014
30601016	Gangrenous stomatitis	J081	J081.00	18116006	30601016
61587014	Vesicular stomatitis	J0801	J080100	36921006	61587014
96292016	Herpetic gingivostomatitis	A542	A542.00	57920007	96292016
395361011	Vesicular stomatitis with xanthem	A743-1	A743.11	266108008	395361011
115028017	Denture stomatitis	J08z2	J08z200	69254008	115028017
254237019	O/E - angular stomatitis	2523	2523.00	163138007	254237019
268763018	Vincent's stomatitis	AA10	AA10.00	173599005	268763018
2673553014	Aphthous stomatitis	J0824	J082400	426965005	2673553014
885671000006119	Angular stomatitis	J0854-99	J085499	279072007	885671000006119

303739017	[X]Other forms of stomatitis	Jyu0C	Jyu0C00	61170000	410501000006111
483231000006114	Angular stomatitis and cheilitis	J0854	J085400	266429005	483231000006114
352258013	Orofacial granulomatosis	J08zB	J08zB00	235048000	352258013
303740015	[X]Other and unspecified lesions of oral mucosa	Jyu0D	Jyu0D00	41188003	406611000006110
14363012	Eosinophilic granuloma of oral mucosa	J08z5	J08z500	8090002	14363012
54885011	Oral submucosal fibrosis	J088	J088.00	32883009	54885011
36678017	Irritative hyperplasia of oral mucosa	J08z6	J08z600	21863002	36678017
127534016	Pyogenic granuloma of oral mucosa	J08z7	J08z700	76813008	127534016
1662701000006110	Dental recall - mucosal lesion present	EMISD_DE213		1662701000006100	1662701000006110
302268010	Oral aphthae NOS	J082z	J082z00	426965005	42291000006118
512092011	Stomatitis	J080	J080.00	61170000	101654014
302246017	Stomatitis NOS	J080z	J080z00	61170000	128081000006115
1490680010	Oral aphthae	J082	J082.00	426965005	2673550012
352406017	Cheilitis granulomatosa	J085F-1	J085F11	235136001	352406017
1816361000006110	Ulcerative oral mucositis	J08zF-1	J08zF11	450005	2462981000000120
222871000000118	Stomatitis - herpetic	A542-2	A542.12	57920007	222871000000118
1805651000006110	O/E - mouth lesion	JHCOE1		1805651000006110	1805651000006110

Appendix E

Behcet's disease Read code list

MedCodeId	Term	Original ReadCode	Cleansed ReadCode	SnomedCT ConceptId	SnomedCTDescriptionId
104572011	Arthropathy in Behcet's syndrome	N012	N012.00	62918002	104572011
454287012	Behcet's syndrome	AD61	AD61.00	310701003	454287012
309488010	Arthropathy in Behcet's syndrome of the lower leg	N0126	N012600	62918002	492901000006117
309484012	Arthropathy in Behcet's syndrome of the upper arm	N0122	N012200	201485008	492931000006113
309489019	Arthropathy in Behcet's syndrome of the ankle and foot	N0127	N012700	201491005	309489019
309485013	Arthropathy in Behcet's syndrome of the forearm	N0123	N012300	62918002	492881000006119
309486014	Arthropathy in Behcet's syndrome of the hand	N0124	N012400	201488005	309486014
309492015	Arthropathy in Behcet's syndrome NOS	N012z	N012z00	62918002	492841000006113
309491010	Arthropathy in Behcet's syndrome of other specified sites	N012y	N012y00	62918002	492861000006112
309490011	Arthropathy in Behcet's syndrome of multiple sites	N012x	N012x00	201492003	309490011
499415017	Behcet's syndrome arthropathy	N0120-1	N012011	62918002	499415017
492911000006119	Arthropathy in Behcet's syndrome of the pelvis/thigh	N0125	N012500	201489002	492911000006119
304769016	Ulceration of vulva in Behcet's disease	K4252	K425200	198231000	304769016
309483018	Arthropathy in Behcet's syndrome of the shoulder region	N0121	N012100	201485008	309483018
400165012	Arthropathy in Behcet's syndrome of unspecified site	N0120	N012000	62918002	492941000006115

Appendix F

IBD Read code list

MedCodeId	Term	Original ReadCode	Cleansed ReadCode	SnomedCT ConceptId	SnomedCT DescriptionId
2579429013	Idiopathic proctocolitis	J41..00		2579429013	64766004
72962011	Mucous colitis and/or proctitis	J41..11		696071000000000	43752006
435370011	Ulcerative colitis and/or proctitis	J41..12		85931000000000	295046003
435370011	Ulcerative proctocolitis	J410.00		435370011	295046003
302953018	Ulcerative ileocolitis	J410000		302953018	196987008
107644019	Ulcerative colitis	J410100		107644019	64766004
496332018	Ulcerative rectosigmoiditis	J410200		496332018	52506002
496249010	Ulcerative proctitis	J410300		496249010	52231000
2532953017	Exacerbation of ulcerative colitis	J410400		2532953017	414156000
435370011	Ulcerative proctocolitis NOS	J410z00		302956014	295046003
353357011	Ulcerative (chronic) enterocolitis	J411.00		85891000000000	235714007
302953018	Ulcerative (chronic) ileocolitis	J412.00		85901000000000	196987008
2872721013	Ulcerative pancolitis	J413.00		2872721013	444548001
2576688010	Other idiopathic proctocolitis	J41y.00		302959019	418130002
2576688010	Other idiopathic proctocolitis NOS	J41yz00		302961011	418130002
2579429013	Idiopathic proctocolitis NOS	J41z.00		302962016	64766004
107644019	[X]Other ulcerative colitis	Jyu4100		303762015	64766004
309743013	Arthropathy in ulcerative colitis	N031000		309743013	201727001
309836013	Juvenile arthritis in ulcerative colitis	N045400		309836013	201807008
56765016	Crohn's disease	J40-1	J40..11	34000006	56765016
302940016	Crohn's disease of the ileum NOS	J4004	J400400	38106008	601051000006114
886291000006112	Regional enteritis - Crohn	J40-99	J40..99	34000006	886291000006112
303761010	[X]Other Crohn's disease	Jyu40	Jyu4000	34000006	408561000006111
309744019	Arthropathy in Crohn's disease	N0311	N031100	201728006	309744019
309833017	Juvenile arthritis in Crohn's disease	N0453	N045300	201805000	309833017
1222351011	Crohn's disease NOS	J40z-1	J40z.11	34000006	841421000006112
2532950019	Exacerbation of Crohn's disease of large intestine	J4012	J401200	414153008	2532950019

179501000006113	Regional enteritis - Crohn's disease	J40	J40..00	34000006	179501000006113
302322010	Orofacial Crohn's disease	J08z9	J08z900	196578009	302322010
302941017	Crohn's disease of the small bowel NOS	J400z	J400z00	56689002	601081000006118
601091000006115	Crohn's disease of the terminal ileum	J4002	J400200	196977009	601091000006115
906051000006118	[RFC] Crohns disease	HNG0087		906051000006102	906051000006118
601031000006119	Crohn's colitis	J401z-1	J401z11	50440006	601031000006119
302939018	Crohn's disease of the ileum unspecified	J4003	J400300	38106008	601061000006111
396357012	Crohn's disease of the large bowel NOS	J401z	J401z00	7620006	601071000006116
2532958014	Exacerbation of Crohn's disease of small intestine	J4005	J400500	414154002	2532958014
302947018	Regional enteritis NOS	J40z	J40z.00	34000006	179511000006111
302937016	Regional enteritis of the jejunum	J4001	J400100	196976000	302937016
497569010	Regional enteritis of the duodenum	J4000	J400000	56287005	497569010
179571000006119	Regional enteritis of the small bowel	J400	J400.00	56689002	179571000006119
488238014	Regional enteritis of the rectum	J4011	J401100	3815005	488238014
1495442018	Regional enteritis of the large bowel	J401	J401.00	7620006	1495442018
179521000006115	Regional enteritis of the colon	J4010	J401000	50440006	179521000006115
302946010	Regional ileocolitis	J402	J402.00	196983007	302946010
2269901000000110	Management of IBD (inflammatory bowel disease)	8Cc5-1	8Cc5.11	700104004	1885481000006120
41137017	Inflammatory bowel disease	J4-2	J4...12	24526004	41137017
2338581000000110	Dietary education for inflammatory bowel disease	8CA4W	8CA4W00	909671000000101	2338581000000110
2269891000000120	Management of inflammatory bowel disease	8Cc5	8Cc5.00	700104004	2989471019

Appendix G

SLE Read code list

MedCodeId	Term	Original ReadCode	Cleansed ReadCode	SnomedCT ConceptId	SnomedCT DescriptionId
92209015	Disseminated lupus erythematosus	N0000	N000000	55464009	92209015
92208011	Systemic lupus erythematosus	N000	N000.00	55464009	92208011
158372014	Neonatal lupus erythematosus	N0005	N000500	95609003	158372014
158442019	Systemic lupus erythematosus encephalitis	N0006-1	N000611	95644001	158442019
297542011	Polyneuropathy in disseminated lupus erythematosus	F3710	F371000	193178008	297542011
297639014	Myopathy due to disseminated lupus erythematosus	F3961	F396100	193248005	297639014
301721015	Lung disease with systemic lupus erythematosus	H57y4	H57y400	196138005	301721015
309408013	Systemic lupus erythematosus NOS	N000z	N000z00	55464009	114241000006115
312579010	[X]Other forms of systemic lupus erythematosus	Nyu43	Nyu4300	55464009	410511000006114
512234017	Cerebral lupus	N0006	N000600	95644001	512234017
359447015	Subacute cutaneous lupus erythematosus	M1547	M154700	239891002	359447015
453243010	Systemic lupus erythematosus with pericarditis	N0004	N000400	309762007	453243010
309383019	[X]Other local lupus erythematosus	Myu78	Myu7800	7119001	411491000006110
114251000006118	Systemic lupus erythematosus with organ or sys involv	N0003	N000300	239887007	114251000006118
677561000006119	Nephrotic syndrome in systemic lupus erythematosus	K01x4	K01x400	68815009	677561000006119
1728151000006120	Systemic lupus erythematosus encephalitis	EMISNQSY6		1728151000006100	1728151000006120
177301000006114	Renal tubulo-interstitial disorder in SLE	K0B40	K0B4000	307755009	177301000006114
114310015	Lupus nephritis	K01x4-1	K01x411	68815009	114310015
308697013	Lupus erythematosus	M154	M154.00	200936003	308697013
308709013	Lupus erythematosus NOS	M154z	M154z00	200936003	732141000006115
308700012	Lupus erythematosus chronicus	M1540	M154000	200937007	308700012
308704015	Lupus erythematosus migrans	M1542	M154200	200939005	308704015
308705019	Lupus erythematosus nodularis	M1543	M154300	200940007	308705019
308707010	Lupus erythematosus unguium mutilans	M1546	M154600	200942004	308707010