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Original article

Incidence and prevalence of juvenile idiopathic arthritis in the United Kingdom, 2000–2018: results from the Clinical Practice Research Datalink

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Abstract

Objective. The incidence and prevalence of JIA was last estimated in the UK in 1994. Since then the disease has been reclassified, the specialty of paediatric rheumatology has evolved and there has been a significant shift in disease management with new advanced therapies. This study aimed to provide up-to-date national estimates of this disease.

Methods. Children and young people (CYP) with JIA were identified in the Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases, which source data from the two most commonly used primary care electronic health record systems in the UK. These databases were combined and the cohort was identified (2000–18) using predefined code lists. Validation was performed through linkage to the England Hospital Episode Statistics. Annual incidence and prevalence rates were calculated and stratified by gender, age group and nation of the UK. Direct standardization to the UK population was performed and 5 year incidence rates were calculated between 2003 and 2018.

Results. The age-standardized incidence rate was 5.61 per 100 000 population. The age-standardized prevalence rate in 2018 was 43.5 per 100 000. Rates were higher in Scotland compared with England: incidence rate ratio 1.27 (95% CI 1.11, 1.46). The 5 year incidence rates did not change significantly over time.

Conclusions. This study has provided the first contemporaneous estimates of occurrence of JIA in the UK in 25 years. These data provide important estimates to inform resource allocation and health service development for management of JIA.

Key words: juvenile idiopathic arthritis, epidemiology, incidence, prevalence, inflammatory arthritis, disease occurrence

CLINICAL SCIENCE

Rheumatology key messages

- This study update estimates of incidence and prevalence of JIA in the UK for the first time in 25 years.
- Rates of JIA have not changed markedly over 15 years and may be higher in Scotland compared with the rest of the UK.
- These results are vital for appropriate resource allocation and provision of rheumatological services for children and young people.

Introduction

JIA encompasses all chronic inflammatory arthritis of unknown aetiology with an onset age of <16 years (1). It can be associated with significant disability and long-term damage to joints as well as comorbidities such as uveitis. Estimates of the occurrence of JIA vary considerably between countries, e.g. incidence ranges from 1.6 to 23 per 100 000 (2). In the UK, the incidence of inflammatory arthritis in children was last estimated in 1990–94. The study used the now defunct European

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classification criteria for juvenile chronic arthritis (JCA) to define the disease, but also included children with seropositive polyarticular disease, who were usually excluded from the JCA definition, reporting rates of 10 per 100 000 children (3). Not only are these data >25 years old, there are a number of other reasons that necessitated re-estimation of the incidence and prevalence of JIA with contemporaneous data. First, terminology to describe the disease has changed; in particular, the International League Against Rheumatism (ILAR) developed new classification criteria for the disease, dividing it into seven distinct subtypes, instead of the three subtypes of previous criteria sets (1). Further, since 1994 the specialty of paediatric rheumatology has emerged in the UK in its own right, independent from general paediatrics and adult rheumatology. Finally, there has been a complete revolution in the management of JIA with the advent of biologic DMARDs (4). These are expensive therapies, therefore accurate and up-to-date measures of disease occurrence are critical for resource, workforce and health service planning. Thus this study aimed to estimate UK national JIA incidence and prevalence rates, identifying any change over time and stratifying by age, gender and the four nations of the UK.

Methods

Setting

The study used data from the Clinical Practice Research Datalink (CPRD), a large primary care database of routinely collected UK electronic health data. The CPRD comprises two separate databases: CRPD GOLD and CPRD Aurum, which capture data from different general practitioner (GP) software platforms. CPRD GOLD includes data from practices using Vision software and covers the whole of the UK. CPRD Aurum includes data from practices using EMIS software and covers England only. Both databases have been shown to be broadly representative of the general population (5, 6). The databases were combined to provide a single dataset covering both the GOLD and Aurum practices. Some practices switched from Vision to EMIS software during the study and appear in both databases. For these patients, only data from Aurum were used, both in identification of cases and the background population comprising incidence or prevalence rate denominator. The study period was from 1 January 2000 to 31 December 2018. The CPRD has pre-existing ethical approval from a National Research Ethics Service Committee, which covers all observational research using anonymized CPRD data such as this study. The study was approved by the CPRD ISAC approval system (protocol number 19_060).

Study population

In both databases, the study population was children and young people (CYP) <16 years of age. CYP were included from the time their GP practice met CPRD research data quality standards, the date they joined the practice or 1 January 2000 until the earliest date of leaving their practice, death, age 16 or the end of the study period. Only the year of birth is available in the datasets, therefore all CYP were assigned 1 January as their date of birth.

Case definition and validation

Cases were patients with a JIA code prior to age 16. Two Read code lists were developed in conjunction with three rheumatologists, including one paediatric rheumatologist, to define cases. These code lists identified codes that could describe any of the ILAR subtypes. The first comprised a broad list of generic codes such as those for 'arthritis', as well as specific codes such as 'juvenile rheumatoid arthritis' and adult descriptions of disease such as 'ankylosing spondylitis' and 'rheumatoid arthritis'. The second code list contained the specific codes for JIA only (code lists are in Supplementary Table S1, available at *Rheumatology* online). Cases were considered incident if they had at least 1 year of registration prior to their first code, unless they were <2 years old when they were considered incident, regardless of the length of time registered at the practice. If a case had less than 1 year of registration at the practice prior to the first code, the case was considered a prevalent case.

In order to validate the cases, the CPRD provided linkages to England Hospital Episode Statistics (HES), which was available for the subset of patients after 2003 whose practices consented to linkage. This dataset contains details of all inpatient admissions and outpatient clinic attendance at English hospitals. Inpatient admissions are coded using the International Classification of Diseases (ICD) systems. Outpatient clinics have fewer details but code the date and specialty of the clinic attended. In the UK, all paediatric rheumatology is delivered through hospital outpatient clinics and inpatient care, including day case admissions for intra-articular steroid injection and treatment given by i.v. infusions. Community clinics and private practice are rare. Therefore linkage to HES should provide near-complete capture of cases in England. A case was considered validated if the patient had either an inpatient admission with an ICD-10 code for JIA (M08) or had at least three outpatient appointments in either paediatric or adult rheumatology. Validated cases were identified from the broad code list to avoid missing CYP who were only given a general/symptom code by their GPs (e.g. 'arthritis') despite regular contact with rheumatology, which would not occur for CYP with non-inflammatory joint pain.

Statistical analysis

The characteristics of the CYP who met our case definitions were tabulated. Incidence rates, overall and stratified by age, gender and region of the UK (provided by the CPRD), were calculated as the number of new cases per 1000 person-years. Incidence rate ratios (IRRs) were calculated to compare incidence rates in the devolved nations to the England incidence rate. Point prevalence was calculated on 31 December each year. The

denominator was the number of CYP who continue to be registered in their GP practise on 31 December each year. The prevalence numerator was CYP who were being followed-up with a JIA code on or prior to 31 December. Incidence and prevalence rates were calculated for the broad and specific code lists as well as limited to the HES validated cases only. Direct standardization was used to determine age-standardized incidence and prevalence rates. Incidence rates were standardized to the England Office for National Statistics mid-year UK population estimates for 2018.

Results

A total of 7 178 119 CYP were included, with 2 688 711 CYP from CPRD Gold and 4 489 408 CYP from CPRD Aurum. Overall, 48.2% were female (Supplementary Table S2, available at *Rheumatology* online).

Cases identified

There were a total of 4331 cases of JIA using the broad code list definition and 2705 cases using the specific code list (Table 1 and Fig. 1). As stated above, HES linkage was available only for CYP in England. From the broad code list cases, HES linkage was available for 2897 cases, of whom 1649 (56.9%) met validation criteria.

Characteristics of cases

For all case definitions, the first JIA code occurred, on average, between 8 and 9 years of age {broad code list: median 9.09 years [interquartile range (IQR) 4.47–12.71]}. Validated cases were marginally younger on average (Table 1). Cases were more frequently female (57.0% female) and the proportion of female CYP increased with both the specific code list (61.6% female) and validated cases (63.6% female) (Table 1). The distribution of CYP with JIA by region reflected the general distribution of the UK population (Supplementary Table S2, available at *Rheumatology* online).

Incidence rates

Incidence rates varied according to broad/specific code lists and validation ranged from 5.88 to 10.96 per 100 000 population (Table 2 and Fig. 2). As might be expected, the broad unvalidated case definition produced the highest estimates. Incidence was higher in females compared with males: specific code list incidence rate 8.75 (95% CI 8.34, 9.18) and 5.07 (4.77, 5.38), respectively. This pattern was also seen in the validated cases where female *vs* male incidence rates were 7.77 (95% CI 7.32, 8.26) *vs* 4.12 (3.81, 4.47).

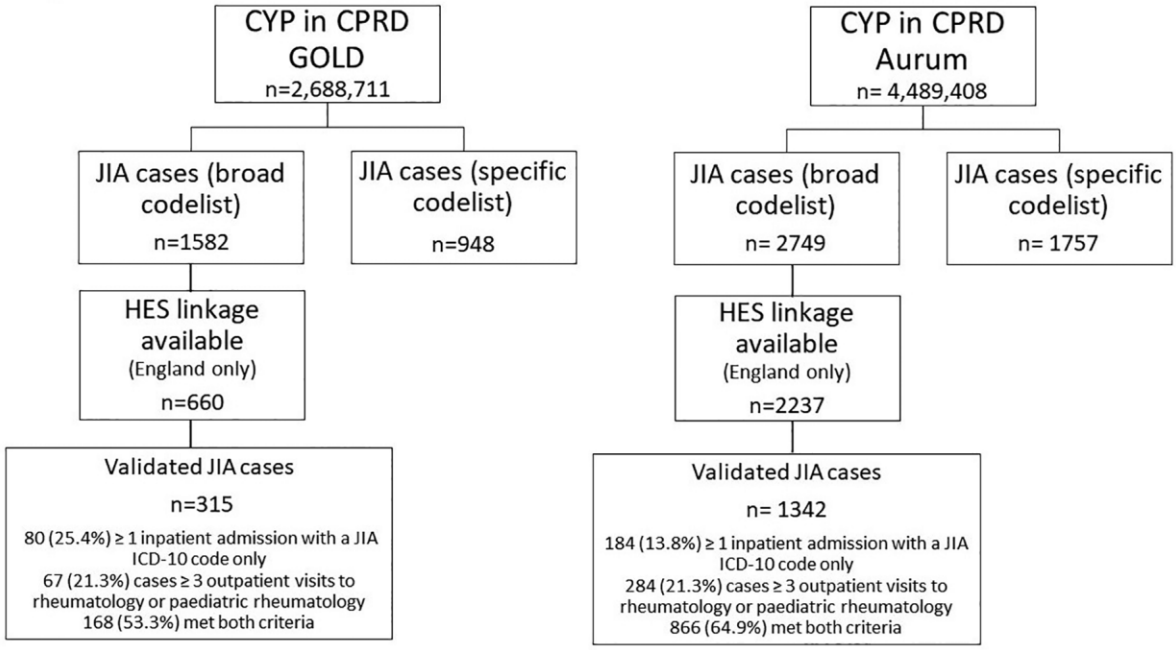
Incidence appeared to increase with age (Figure 3a), with a slightly lower rate in middle childhood. There was no evidence of a change in incidence over time (Figure 3b). Looking at the four nations of the UK, Scotland appeared to have higher incidence of JIA compared with the other nations (Figure 3c), and this was borne out by the IRRs. These showed significantly lower IRRs in Northern Ireland and Wales compared with England: IRR 0.69 (95% CI 0.50, 0.94) and 0.73 (0.61, 0.88), respectively. In contrast, Scotland was significantly higher than England, with an IRR of 1.27 (95% CI 1.11, 1.46). The 2018 age-standardized incidence was 5.61 per 100 000 population using validated cases.

Table 1 Baseline characteristics of cases

Characteristics		Broad code list	Specific code list	Validated cases[a]
n		4331	2705	1649
Age first code, years, median (IQR)		9.09 (4.47–12.71)	9.00 (4.00–12.00)	8.49 (4.20–12.05)
Gender, *n* (%)	Male	1862 (43.0)	1039 (38.4)	601 (36.4)
	Female	2469 (57.0)	1666 (61.6)	1048 (63.6)
Region of UK, *n* (%)	North East	176 (4.1)	120 (4.4)	101 (6.1)
	North West	548 (12.7)	331 (12.3)	269 (16.3)
	Yorkshire and the Humber	153 (3.5)	108 (4.0)	77 (4.7)
	East Midlands	105 (2.4)	60 (2.2)	33 (2.0)
	West Midlands	661 (15.3)	394 (14.6)	302 (18.3)
	East of England	270 (6.2)	159 (5.9)	105 (6.4)
	South West	548 (12.7)	364 (13.5)	255 (15.5)
	South Central	450 (10.4)	294 (10.9)	193 (11.7)
	London	501 (11.6)	306 (11.3)	189 (11.5)
	South East Coast	308 (7.1)	175 (6.5)	125 (7.6)
	Northern Ireland	62 (1.4)	39 (1.4)	–
	Scotland	343 (7.9)	236 (8.7)	–
	Wales	202 (4.7)	115 (4.3)	–

[a]Validated cases were identified from the broad code list (see Fig. 1).

Fig. 1 Case identification and validation flowchart



Flowchart shows how cases of JIA were identified and validated in the study.

Table 2 Incidence rates of JIA

Code list	Person-years	Cases, *n*	Incidence rate (95% CI)
Broad code list	39 533 815	4331	10.96 (10.63, 11.29)
Specific code list	39 541 603	2705	6.84 (6.59, 7.1)
Validated cases[a]	28 057 307	1649	5.88 (5.60, 6.17)

[a]Validated cases were identified from the broad code list (see Fig. 1).

Prevalence

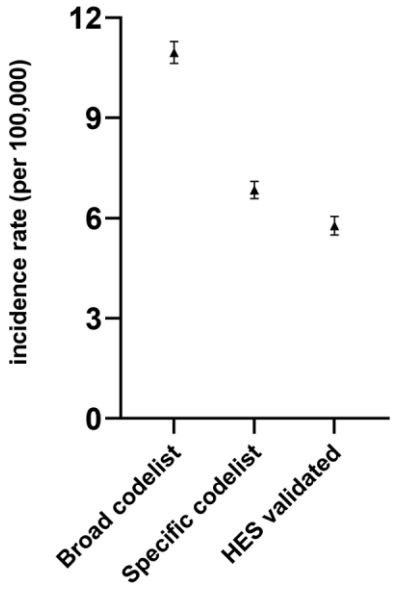
Prevalence rates also varied by broad/specific code list and validated cases. In 2018 rates ranged from 31 per 100 000 to 85 per 100 000 (Table 3). Prevalence increased over time from 2000 to 2010 in CPRD GOLD and then plateaued (Fig. 4). The 2018 age-standardized prevalence rate was 43.5 per 100 000 using validated cases.

Discussion

This study has provided the first estimates of the incidence and prevalence of JIA in the UK this century and the first estimates for nearly 25 years. The overall age-standardized incidence was 5.61 per 100 000 and the 2018 age-standardized prevalence rate was 43.5 per 100 000.

In a national primary care dataset, we showed that the incidence of JIA in the UK appears to be stable over time but varies by age. Incidence followed a bimodal distribution, with a dip in incidence in middle childhood, as has been shown in other datasets (7). The absence of change over time in our study is similar to incidence data from Manitoba, Canada, where Shiff *et al.* (8) did not identify any change in incidence from 2000 to 2011, but is in slight contrast with the most recent data from the USA. In a study from the Rochester Epidemiology Project, Krause *et al.* (9) showed stable average incidence over time but identified cyclical peaks in incidence every 10 years. It may be that the follow-up time in our study was insufficient to identify these peaks. In our data, prevalence rates did appear to increase over time in the first part of the study period, and this was particularly notable with the broad code list, and therefore may not reflect changes in true JIA. It is in contrast with data from the Canadian study that showed a decline in prevalence over time. Rates were higher in female CYP, particularly among validated cases. This is in line with the international Epidemiology, treatment and Outcome of Childhood Arthritis study, which phenotyped patients with JIA recruited from specialist centres to identify regional differences (10). The UK was considered part of Western Europe in their study, which found

Fig. 2 Incidence rates by code list

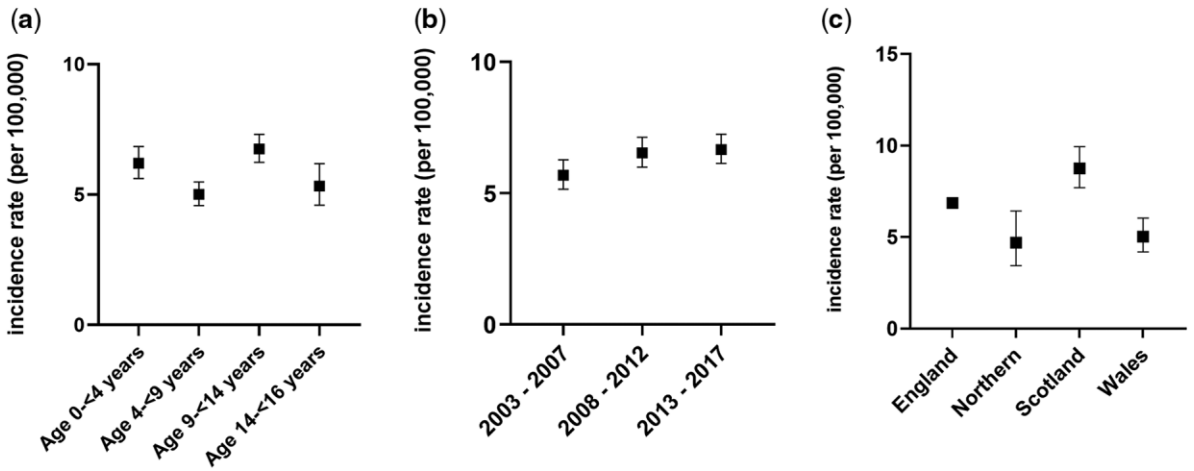


The incidence rate of JIA and 95% CIs for each code list type.

a similar proportion of female participants in that region; interestingly, this proportion was lower than other global regions. This may reflect differing prevalence of subtypes and differing underlying genetic risk factors.

Estimates are slightly lower than the previous data from 1990–94 (3), which may represent a true decrease in the incidence of inflammatory arthritis in CYP. Nevertheless, we did not see any change in incidence of JIA over a period of 15 years in this study, thus it would seem unusual that cases should drop from 1994 to 2000 and then level off. It should be noted that the previous estimates were in an era of older classification criteria of JIA, which may have influenced case definition. Further, they were based on tertiary centre cases within a defined population. Given the nature of tertiary centres, even with careful checking, there may have been an overestimation of the numerator and additional cases included from outside the area. Equally, our study may be an underestimate, if some cases were seen in secondary care and never given a diagnostic code in their GP record. However, we attempted to address this by using a broad initial code list (likely not sufficiently specific on its own) and validating cases by linkage to secondary care. Interestingly, over a similar time period and also within the CPRD, rates of adult RA have been

Fig. 3 Incidence rates by age group, time period and country



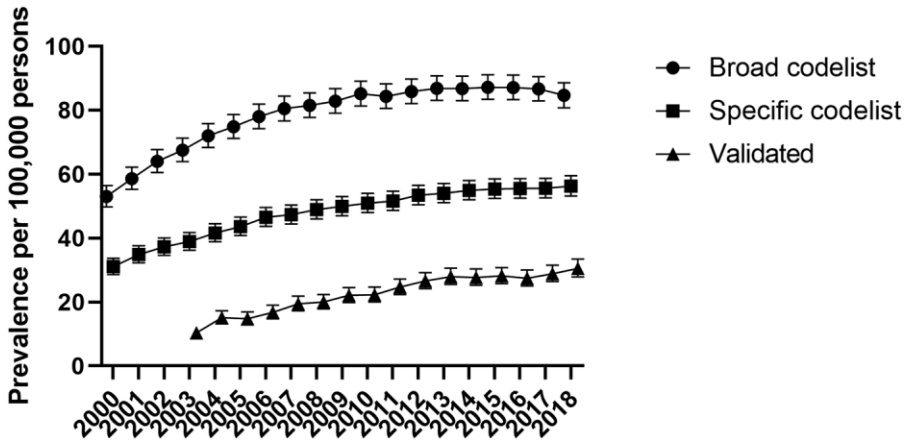
The incidence rates of JIA and 95% CIs stratified by (**a**) age, (**b**) time period and (**c**) country. For (a) and (b), cases were identified using the validated code list. (c) uses data from CPRD GOLD only and cases were identified using the specific code list.

Table 3 Prevalence rates per 100 000 in 2018

Code list	Cases, *n*	Denominator	Prevalence rate (95% CI)
Broad code list	1826	2 156 639	84.67 (80.83, 88.64)
Specific code list	1214	2 156 639	56.29 (53.17, 59.55)
Validated cases[a]	471	1 541 851	30.55 (27.85, 33.43)

[a]Validated cases identified from the broad code list.

FIG. 4 Prevalence rates by code list type



The prevalence rates of JIA and 95% CIs over time for each code list type.

shown to be decreasing (11). Although they are different diseases, they could be considered to have similar aetiology, and this suggests the cause of the decrease seen in RA is not driving an overall decrease in autoimmune inflammatory arthritides.

Regionally across the UK, rates of JIA were higher in our study in Scotland compared with England, and slightly lower in Wales, with the number of cases in Northern Ireland being too small to definitively identify a difference. In Europe, other studies have shown higher rates of JIA in more northern countries, therefore our data may represent the more northerly latitude of Scotland (2). The rates in Scotland were closer to those of Scandinavia (12), whereas rates in other parts of the UK more closely matched reports from France and Spain (13, 14). Another possible explanation is surveillance bias, where greater numbers of cases are seen because of increased awareness of the disease. In the UK there were only a limited number of paediatric rheumatology centres for many years, with most patients with what is now called JIA being treated either in general paediatrics or adult rheumatology clinics. The specialty of paediatric rheumatology was officially recognized by the Royal College of Paediatrics and Child Health in 2005 (15), and Scotland developed the first paediatric rheumatology network in the UK in 2009, thus the increased awareness from this in Scotland may have led to increased rates. Notably, as recently as 2016, Wales did not have dedicated tertiary centre for paediatric rheumatology (16) and thus detection bias may also have contributed to their lower rates. Nevertheless, the trend of higher rates in Scotland were seen in both the broad and specific code lists, which would suggest there may be a true difference in incidence.

The strengths of this study lie in the use of a national primary care dataset of routinely collected data. This provides broad and representative coverage of the entire nation. However, there were also a number of limitations. There are no Read code lists that accurately correspond to the ILAR subtypes, therefore we were unable to provide a breakdown of incidence by subtype. Although some codes exist for oligo- or pauci-articular juvenile arthritis, we could not guarantee that all cases of the oligoarthritis subtype as defined by ILAR would be captured by these and no relevant codes were available for a number of the ILAR subtypes. Given the purpose of this study was to estimate incidence and prevalence, these would be inadequate. The age at diagnosis presented may have been lagged, as JIA diagnosis requires specialist input and there may have been a delay in diagnostic confirmation (via discharge or outpatient letters to the GP) being entered into the primary care record. Further, the specialist input required for diagnosis means there is the potential for misclassification bias using primary care data. Our use of HES-linked data to validate cases was able to address this misclassification, however, this was only available for cases in England. Nevertheless, incidence and prevalence rates using the specific Read code list were very similar to those produced using the HES validated cases, providing reassurance that these definitions are capturing cases with good accuracy. This is in line with previous research in the CPRD, which found that using a Read code list that matched the definition of JIA or its ILAR subtypes as closely as possible (such as our specific code list), provided >90% sensitivity and specificity (17).

In conclusion, this study provides up-to-date data on the incidence and prevalence of JIA in the UK. Such data are important to underpin paediatric rheumatology services and plan for optimal care for patients with JIA.

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Data availability statement

The data in this article were sourced from the CPRD, which is jointly sponsored by the Medicines and Health Regulatory Agency and the NIHR. The data can be accessed by application to the CPRD at https://www.cprd.com, where the protocol used to create the dataset for this study can also be found.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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