Increasing Incidence of Juvenile Idiopathic Arthritis: A Trend Over 31 Years in Southern Sweden

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Short Report

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Abstract

Background The reported incidence of juvenile idiopathic arthritis (JIA) varies from studies around the world, depending on patient collection techniques, geographic region, and time. Our aim was to study the mean annual incidence of juvenile arthritis in a population-based setting using two regional cohorts of children diagnosed with juvenile chronic arthritis (JCA) and JIA over a period of 31 years.

Findings The study population was 651 children diagnosed 1980-2010. The mean annual incidence over the period was 9.9 per 100,000 children, with a range from 4.2 per 100,000 in 1980 to 17.1 per 100,000 children in 2010. When comparing incidence rate between the decade of diagnosis using rate ratios, there is a significant difference with diagnosis 1980-1989 as comparator.

Conclusions We show a statistically significant increase in the incidence of JIA over three decades in a population-based cohort of children with juvenile arthritis.

Background

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and is considered a chronic disease (1), although studies on long-term outcome suggest approximately 50% remission rate in adults (2–4). The incidence is reported to be between 3.1 – 15.0/100 000 children depending on geographic region and study design. (5–10) In Skåne, the southernmost region of Sweden, the mean yearly incidence of JIA was 12.8/100 000 children 2002-2010 (11). A trend of increasing incidence of chronic immune disease, such as juvenile arthritis, has been observed in Denmark over 35 years (12).

In our previously published population-based JIA cohort (11), we analyzed the regional incidence rate 2002-2010. We now aimed to investigate if there was an increasing annual incidence of JIA over a longer period and thus created a cohort of children in the same South-Swedish region, diagnosed with juvenile arthritis 1980-2001.

Methods

Case collection

The study area was Skåne, the southernmost region in Sweden, with 12.3% (1 023 479) of the Swedish population by December 1980 and 13.3% (1 377 827) by December 2019. Children (0-15 years) constituted 20.7% and 19.4% of the population in Skåne in 1980 and 2019 respectively(13). Cases were collected through a search for healthcare contacts 1980-2001 with an International Classification of Diseases (ICD)-code for JIA or juvenile chronic arthritis (JCA) in Skåne, both from the local clinical database at the regional center for pediatric rheumatology, Skåne University Hospital in Lund, and the diagnosis register at the National Board for Health and Welfare (NBWH). For the cases collected from the NBHW, medical records were reviewed to ensure correct diagnosis and a patient was included in the cohort if considered diagnosed correctly before the 16th birthday between 1 January 1980 and 31

December 2001 while living in Skåne. Subgroup classification was made according to International League of Associations for Rheumatology (ILAR) definitions.

The cases from the local search were included if they fulfilled the age and geographic criteria, and if a rheumatologist diagnosed the child with an unambiguous pediatric arthritic disease with symptom duration longer than three months, according to the European Alliance of Associations for Rheumatology (EULAR) definition for JCA. If a case was considered uncertain the diagnosis was validated through review of the medical record. At cohort inclusion the diagnostic subgroup was adapted to the ILAR definition.

The study was approved by the Regional Ethical Review Board for southern Sweden (2013/192 and 2015/62) and the National Ethical Review Agency (2020-02935).

Data collection

Demographic data, occurrence of uveitis and pharmacological treatment was recorded through medical record review. Treatment option was registered annually. Patients were followed until migration, death, loss to follow-up or end of the study period on December 31st 2015, whichever occurred first.

Registration of deaths and cause of death is mandatory in Sweden. Data on cause of death was obtained from the National cause of death register between 1 January 1980 and 31 December 2019. The individual data obtained was date of death, ICD-codes for the main cause of death and medical conditions contributing to the cause of death.

Statistical analysis

Demographics was analyzed descriptively. Incidence rate was calculated using the number of incident cases as numerator and the pediatric population at risk as denominator. 95% confidence interval of the incidence rate and rate ratio with incident cases summarized by decade due to the limited number of cases, were calculated using openepi.com(14).

Mortality rate was calculated using the deceased as numerator and the number of individuals in the cohort at risk the corresponding year as denominator. For comparison with the general population in Skåne we obtained the annual number of deaths in the age group in question and the number of people at risk from the public registry, Statistics Sweden(13). Statistical analyses were performed using IBM® SPSS® Statistics version 27 for Macintosh.

Results

Patient characteristics

In total, 721 individuals with a registered ICD-code for JIA or JCA were found. 55 medical records could not be found, and an additional 266 individuals were excluded, resulting in a cohort of 400 children

diagnosed with juvenile arthritis 1980-2001 while living in the study area. (*A detailed description of the case collection process and reasons for exclusion is enclosed as Additional file 1.*)

Two thirds (67.3%) of the children were female and median age at diagnosis was 8.1 years (n=394). In six cases a specified date for diagnosis was not recorded. The children were followed for a median time of 8.2 years (range 0-34.6) (n=384).

Oligoarticular JIA was the largest subgroup (55.3%) and undifferentiated JIA the smallest (3.3%).

A total of 14.0% of the children were at some point during their disease course diagnosed with anterior uveitis, 9.6% as acute uveitis and 8.5% as chronic uveitis.

Almost half of the group (46.8%) were treated with conventional disease-modifying antirheumatic drugs (DMARD) and 14.5% were prescribed biological DMARDs. (Table 1)

Table 1
Demographics and treatment

	Total (n 400)	Oligoarthritis (n 221)	RF- (n 72)	RF+ (n 19)	soJIA (n 19)	ERA (n 26)	JPsA (n 30)	uJIA (n 13)
Female (%)	67.3	67.9	75.0	84.2	52.6	38.5	70.0	61.5
Age at diagnosis (years (25-75 centiles))	8.1 (4.0 – 12.4)	6.5 (3.6 – 11.0)	8.9 (4.3 – 12.7)	14.1 (10.2 – 15.6)	3.8 (2.1 – 7.9)	12.1 (10.3 –14.7)	12.5 (5.8 – 14.1)	4.8 (3.1 – 11.2)
Follow-up time (years (25-75 centiles))	8.2 (5.1 – 12.3)	8.8 (4.0 – 14.1)	11.2 (5.8 – 17.0)	14.4 (7.0 – 22.0)	13.0 (9.1 – 16.6)	8.3 (4.8 – 14.8)	8.3 (5.1 – 12.4)	19.0 (6.4 – 22.9)
Uveitis (%)	14	16.3	13.9	0	0	7.7	6.7	46.2
Chronic uveitis (%)	8.5	11.3	8.3	0	0	0	0	23.1
Acute uveitis (%)	9.5	10.4	8.3	0	0	7.7	6.7	38.5
Treatment (%)								
Oral glucocorticoids	46.0	30.8	65.3	84.2	94.7	57.7	50.0	38.5
cDMARDs	46.8	33.9	63.9	100	78.9	50.0	40.0	30.8
Methotrexate	29.8	21.3	40.3	57.9	65.0	15.4	36.7	30.8
bDMARDs	14.5	5.4	22.2	36.8	26.3	15.4	26.7	46.2
TNF-inhibitors	14.3	5.4	22.2	36.8	26.3	15.4	26.7	38.5
Treatment options are presented as the percentage of patients in the subgroups with at least one treatment year.								
Abbreviations: DMARD - disease-modifying antirheumatic drug; TNF - tumor necrosis factor; RF - rheumatoid factor; RF- - RF negative polyarthritis; RF+ - RF positive polyarthritis; soJIA - systemic onset JIA; ERA - enthesitis-related arthritis; JPsA - juvenile psoriatic arthritis; uJIA - undifferentiated JIA								

Incidence

For the calculation of incidence rate, we combined the cases from the current cohort (n=400) with the cases in our previously published cohort (n=251)(11), forming a total study population of 651 individuals.

The mean annual incidence rate of the study period 1980-2010 was 9.9 (95% confidence interval 9.2-10.7) per 100 000 children < 16 years. The yearly incidence rate is increasing throughout the study period, ranging from 4.2 (2.1-7.8) per 100 000 children in 1980 to 17.1 (12.3-23.3) in 2010. (Figure 1)

The rate ratio is statistically significant when comparing the incidence rate in 1980-1989 to the corresponding rate in 1990-1999 (1.43 (95% confidence interval 1.2-1.8)) and 2000-2010 (1.88 (1.5-2.3)).

Mortality rate

The mortality is increased in inflammatory diseases such as rheumatoid arthritis (15, 16) and Crohn's disease(17). However, there are conflicting results regarding mortality in JIA(18–22).

During the study period with 5646 person-years of follow-up, eight individuals died. Only one patient died from complications related to juvenile arthritis. Other causes of death were suicide, traumatic accidents, infection, and diabetes. Compared to the deaths in the general population in the corresponding age range and years, it appears as if the mortality rate is almost tenfold. However, this should be interpreted with great caution. *(A table with comparison of mortality rate is enclosed as Additional file 2.)*

Conclusions

We have collected incident cases of JIA in the Swedish region of Skåne 1980-2001 and calculated the annual incidence rate. Combined with data from our previously published cohort study(11) we show an increasing incidence of JIA since 1980, from 4.2 to 17.1 per 100 000 children under the age of 16.

The demographic data of the cohort are in accordance with our previously published results(11). The prevalence of uveitis is slightly higher, 14% vs 10%, and DMARDs are more widely used in modern JIA treatment, conventional (46.8% vs 64.9%) as well as biological (14.5% vs 23.9%). The adaption of ILAR subgroups to diagnosis according to the EULAR classification criteria used during our study period, makes subgroup categorization less strict, the subgroup of undifferentiated arthritis does not exist in the EULAR criteria for example. Arthritis of unknown cause with duration for at least three months defines a JCA diagnosis according to EULAR, in contrast to six weeks for an ILAR JIA diagnosis. The longer symptom duration might partly explain the lower incidence at the beginning of our study period. However, the ILAR definition was not used until 2001 and the increase occurs throughout the period with significant incidence rate ratio, and not with the cyclicity of incidence peaks every ten years, as shown for juvenile rheumatoid arthritis by others (9).

The low incidence in the first half of the study period might partly be explained by our study only having coverage for inpatient visits, because registration of ICD-codes for outpatient visits were not mandatory in Sweden until 2002. However, in the 1980's most children were, at least at diagnosis, in need of inpatient care for rehabilitation and treatment. Additionally, since approximately 75% of children with JIA in the region at some point during 2002-2010 were treated with intra-articular corticosteroids administered as inpatient care(11) and that was even more common as treatment in the previous decades, we believe that only a few cases are missed due to the lack of registered data. Indeed, our results are supported by the newly reported Danish trend of an increasing incidence of chronic immune diseases(12). The increased incidence might also in part reflect an increased awareness of JIA over time.

The number of deaths among the JIA patients was low (n=8), thus further statistical analysis was not done. The increased relative mortality rate must be interpreted with great caution due to the low number of cases and although increased, we cannot conclude that there was an excess mortality in the JIA patients. To study the mortality in JIA there is a need for larger cohorts and longer follow-up period.

In conclusion, we show an increasing incidence of JIA over a period of 31 years. Further studies will be needed to conclude if this is a continuous trend.

Abbreviations

JIA

Juvenile idiopathic arthritis

ICD

International Classification of Diseases

JCA

Juvenile chronic arthritis

NBWH

National Board for Health and Welfare

ILAR

International League of Associations for Rheumatology

EULAR

European Alliance of Associations for Rheumatology

DMARD

Disease-modifying antirheumatic drug

Declarations

Ethics approval and consent to participate

The study was approved by the Regional Ethical Review Board for southern Sweden (2013/192 and 2015/62) and the National Ethical Review Agency (2020-02935).

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during this current study are not publicly available as they contain information that could compromise research participant privacy. The data are available and anonymized from the corresponding author (EB) on reasonable request and appropriate permission from regulatory authorities.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

EB conceptualized the study, acquired, analyzed and interpreted the data and wrote the manuscript. AD and HT assisted in analysis and interpretation of data. BM was one of the initiators in forming the cohort and assisted in the interpretation of the results. RK conceptualized the study and interpreted data. All authors have reviewed and revised the manuscript.

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References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* (London, England). 2007;369(9563):767–78.
2. Glerup M, Rypdal V, Arnstad ED, Ekelund M, Peltoniemi S, Aalto K, et al. Long-term outcomes in juvenile idiopathic arthritis: 18 years of follow-up in the population-based Nordic Juvenile Idiopathic Arthritis (JIA) cohort. *Arthritis care & research*. 2019.
3. Glerup M, Herlin T, Twilt M. Clinical Outcome and Long-term Remission in JIA. *Current rheumatology reports*. 2017;19(12):75.
4. Selvaag AM, Aulie HA, Lilleby V, Flatø B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. *Annals of the rheumatic diseases*. 2016;75(1):190–5.
5. Danner S, Sordet C, Terzic J, Donato L, Velten M, Fischbach M, et al. Epidemiology of juvenile idiopathic arthritis in Alsace, France. *The Journal of rheumatology*. 2006;33(7):1377–81.
6. Modesto C, Antón J, Rodriguez B, Bou R, Arnal C, Ros J, et al. Incidence and prevalence of juvenile idiopathic arthritis in Catalonia (Spain). *Scandinavian journal of rheumatology*. 2010;39(6):472–9.
7. Shiff NJ, Oen K, Kroeker K, Lix LM. Trends in Population-Based Incidence and Prevalence of Juvenile Idiopathic Arthritis in Manitoba, Canada. *Arthritis care & research*. 2019;71(3):413–8.
8. Berntson L, Andersson Gäre B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the

- validity of the ILAR and EULAR criteria. *The Journal of rheumatology*. 2003;30(10):2275–82.
9. Krause ML, Crowson CS, Michet CJ, Mason T, Muskardin TW, Matteson EL. Juvenile Idiopathic Arthritis in Olmsted County, Minnesota, 1960-2013. *Arthritis & rheumatology* (Hoboken, NJ). 2016;68(1):247-54.
 10. Costello R, McDonagh J, Hyrich K, Humphreys J. Incidence and prevalence of Juvenile Idiopathic Arthritis in the United Kingdom 2000-2018: results from the Clinical Practice Research Datalink. *Rheumatology* (Oxford, England). 2021.
 11. Berthold E, Mansson B, Kahn R. Outcome in juvenile idiopathic arthritis: a population-based study from Sweden. *Arthritis research & therapy*. 2019;21(1):218.
 12. Sevelsted A, Chawes B, Stokholm J, Bønnelykke K, Bisgaard H. Time trends of chronic immune diseases by year of birth in Danish registries. *Eur J Epidemiol*. 2021.
 13. Sweden S. Statistical database www.statistikdatabasen.scb.se2021 [Available from: <https://www.statistikdatabasen.scb.se/pxweb/en/ssd/>].
 14. Dean AS, KM; Soe, MM. OpenEpi: Open source epidemiologic statistics for public health. 2013 [updated 2013/04/06. Available from: www.OpenEpi.com.
 15. van den Hoek J, Boshuizen HC, Roorda LD, Tijhuis GJ, Nurmohamed MT, van den Bos GA, et al. Mortality in patients with rheumatoid arthritis: a 15-year prospective cohort study. *Rheumatology international*. 2017;37(4):487–93.
 16. Løgstrup BB, Ellingsen T, Pedersen AB, Darvalics B, Olesen KKW, Bøtker HE, et al. Cardiovascular risk and mortality in rheumatoid arthritis compared with diabetes mellitus and the general population. *Rheumatology* (Oxford, England). 2021;60(3):1400–9.
 17. Burisch J, Munkholm P. The epidemiology of inflammatory bowel disease. *Scandinavian journal of gastroenterology*. 2015;50(8):942–51.
 18. French AR, Mason T, Nelson AM, O'Fallon WM, Gabriel SE. Increased mortality in adults with a history of juvenile rheumatoid arthritis: a population-based study. *Arthritis and rheumatism*. 2001;44(3):523–7.
 19. Thomas E, Symmons DP, Brewster DH, Black RJ, Macfarlane GJ. National study of cause-specific mortality in rheumatoid arthritis, juvenile chronic arthritis, and other rheumatic conditions: a 20 year followup study. *The Journal of rheumatology*. 2003;30(5):958–65.
 20. Hashkes PJ, Wright BM, Lauer MS, Worley SE, Tang AS, Roettcher PA, et al. Mortality outcomes in pediatric rheumatology in the US. *Arthritis and rheumatism*. 2010;62(2):599–608.
 21. Davies R, Southwood T, Kearsley-Fleet L, Lunt M, Baildam E, Beresford MW, et al. Mortality rates are increased in patients with systemic juvenile idiopathic arthritis. *Archives of disease in childhood*. 2017;102(2):206–7.
 22. Kyllonen MS, Kautiainen H, Puolakka K, Vahasalo P. The mortality rate and causes of death among juvenile idiopathic arthritis patients in Finland. *Clinical and experimental rheumatology*. 2019;37(3):508–11.

Figures

Figure 1

Annual incidence rate

Annual incidence rate (dots) with 95 % confidence interval (lines) presented per 100 000 children. The dashed line represents the division of the current (1980-2001) and previously published (2002-2010) cohorts.

Supplementary Files

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