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Incidence and Genetic Risk of Juvenile Idiopathic Arthritis in Norway by Latitude

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Objective. We aimed to investigate the incidence of juvenile idiopathic arthritis (JIA) in the three geographic regions of Norway and whether potential regional incidence differences are explained by environmental or genetic factors across regions.

Methods. We conducted a register-based cohort study including all Norwegian children born from 2004 to 2019, with follow-up throughout 2020. The JIA diagnosis, defined by at least two *International Classification of Diseases, Tenth Revision* codes for JIA, was validated against medical records. The incidence rate (IR) and hazard ratio (HR) for JIA were estimated for all Norway and for the North, Mid, and South regions. In a subsample from the Norwegian Mother, Father, and Child Cohort Study (MoBa), the genetic risk for JIA was assessed in the three regions.

Results. After median 9.1 (range 0.3–16.0) years of follow-up, we identified 1,184 patients with JIA and 910,058 controls. The IR for JIA/100,000 person-years was 14.4 in all of Norway, 25.9 in the North region, 17.9 in the Mid region, and 12.5 in the South region. The HR (95% confidence interval [CI]) of JIA in the North region was 2.07 (1.77–2.43) and in the Mid region HR 1.43 (95% CI 1.23–1.67) compared with the South region. Adjustments for perinatal factors, socioeconomic status, and early antibiotic exposure did not change our estimates substantially. In MoBa (238 patients with JIA, 57,392 controls), the association between JIA and region of birth was no longer significant when adjusting for genetic factors.

Conclusion. We found a higher incidence of JIA with increasing latitude without evidence for available environmental factors explaining the observed gradient. In contrast, genetic factors modified the association, but further studies are warranted.

INTRODUCTION

The term juvenile idiopathic arthritis (JIA) describes a group of clinically heterogeneous diseases with onset before age 16 years, characterized by chronic joint inflammation.[1] Although its etiology is largely unknown, JIA is considered a complex condition in which one or more environmental risk factors may trigger disease in a genetically susceptible individual.[1]

JIA is the most common inflammatory rheumatic condition in childhood,[2] but the estimated incidence varies.[3,4] A systematic review from 2014 reported an incidence rate (IR) for JIA ranging from 1.6 to 23.0 cases per 100,000 person-years (PYs).[3] Some of this variation has previously been explained by differences in research methodology among studies.[4] However, epidemiologic studies still indicate a variation across geographic regions, populations, and ethnicities.[5–8] If there is a true variation across

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geographic regions, characterizing it may aid to identify disease-modifying environmental and genetic factors.

In the United States and Europe, both in the northern hemisphere, several autoimmune diseases show a notable north-south gradient with the highest incidence in the north.[9–11] This pattern is also seen in some childhood-onset autoimmune diseases like type 1 diabetes and pediatric inflammatory bowel disease (PIBD).[9,10] Similarly, in the southern hemisphere, a New Zealand study reported a higher risk of PIBD at higher southern latitudes.[12]

A possible north-south gradient in JIA has also been pointed out with the highest incidence in the northernmost countries in Europe compared with the south.[7,13] Within Norway, previous studies have reported a higher incidence of JIA in the northernmost regions than in the southeast region.[14,15] However, no previous study has investigated JIA incidence across different European countries or all regions in Norway; thus, the results are not directly comparable because of the variation in methodology. Importantly, no previous study has accounted for the effect of genetic or environmental factors on the occurrence of JIA across geographic regions.

Norway is the country situated farthest north in Europe, and it stretches across a wider range of latitudes than most other European countries, from 57°N to 71°N latitude.[16] The geography of Norway and the public health care system,[17] combined with unique health and administrative registries, position Norway as an ideal location for conducting epidemiologic research across geographic regions.

We aimed to investigate the incidence of JIA across different geographic regions in Norway and assess if there is a latitudinal gradient. To explain possible regional differences in the incidence, we also aimed to investigate the impact of environmental or genetic risk factors for JIA across regions.

PATIENTS AND METHODS

Study design, populations, and data sources. To investigate the incidence of JIA in different geographic regions, we conducted a nationwide register-based study based on data from the Medical Birth Registry of Norway (MBRN). To assess the impact of potential differences in genetic background for JIA across regions, we also included data from the Norwegian Mother, Father, and Child Cohort Study (MoBa).

The MBRN sample. From the MBRN (MBRN sample), we included all children born in Norway between January 1, 2004, and December 31, 2019, and observed them until the onset of JIA, age 16 years, or December 31, 2020, whichever occurred first. The MBRN is a national health registry based on mandatory reporting and contains information about all births in Norway.[18] Data from the MBRN were linked on an individual level using the unique national identification (ID) number with data from the Norwegian Patient Registry (NPR), Statistics Norway (SSB), and Norwegian Prescription Database (NorPD). Children who had emigrated were excluded.

The MoBa sample. From MoBa (MoBa sample), we included children who previously had been genotyped in MoBaPsychGen.[19] MoBa is a population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (NIPH). Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 41% of the pregnancies. The cohort included approximately 114,500 children, 95,200 mothers, and 75,200 fathers.[20,21] We used version 12 of the quality-assured MoBa data files, which was released for research purposes in January 2019. Data on the children in MoBa were also linked on an individual level with data from the NPR. The MoBa sample partially overlaps with the MBRN sample; 42,552 children in the MoBa sample were born between 2004 and 2009 and were also included in the MBRN sample.

Study setting. In 2020, the number of inhabitants in Norway was approximately 5.4 million, with almost one million children age <16 years.[22] The health care system provides universal access to health care services, and it is free of charge for children age <16 years.[17] Children with JIA are followed either by pediatricians or rheumatologists, almost exclusively at public hospitals. The university hospitals have the main responsibility for patients with JIA, but many patients also receive intermediate follow-up care at their local hospitals.

Case definition. Cases in the MBRN sample were identified using data from the NPR, which has received data with personal ID numbers from all Norwegian public hospitals and specialists with public funding since 2008.[23] Consequently, the NPR captures data for virtually all Norwegian children with JIA. Cases were defined by at least two *International Classification of Diseases, Tenth Revision* (ICD-10) codes of M08 (juvenile arthritis) and/or M09 (juvenile arthritis in diseases classified elsewhere) reported to the NPR between January 1, 2008, and December 31, 2020, with the first registration before age 16 years. If the year of diagnosis was 2020, we only required one code of M08 or M09 because this was the last year of data from the NPR and some children most likely only had one visit before the end of the year. The age of diagnosis was calculated from the child's birth year and month to the year of their first registration of a relevant ICD-10 code (M08, M09, or M13 [other arthritis]) for those who later fulfilled the case definition. Because we only had information about which year the ICD-10 codes were registered, we averaged the month of onset to July 1. In sensitivity analyses, we also assessed a stricter case definition with at least three codes of M08 and/or M09 (at least two codes if the year of onset was 2020). The cases in the MoBa sample were identified according to the same case definition of at least two diagnostic codes for

JIA using data from the NPR registered between January 1, 2008, and December 2021. If the year of diagnosis was 2021, only one code of M08 or M09 was required.

Validation of the case definition. To assess the validity of our case definition against medical records and to evaluate potential regional variations in coding practices in Norway, we conducted a validation study that included data from four hospitals. Oslo University Hospital (OUS), St. Olav's Hospital, and the University Hospital of North Norway (UNN) are university hospitals with primary responsibility for patients with JIA living in Southeastern, Mid- and Northern Norway, respectively. Vestfold Hospital Trust (SIV) is a local hospital situated southwest of the capital Oslo.

At each hospital, patients age <16 years registered with their first M08 or M09 ICD-10 code between January 1, 2008, and December 31, 2020, were identified. Children who resided outside the primary health region of each hospital and those who were observed in other hospitals with insufficient information available in their medical records were excluded. At OUS, a random sample from the pediatric and rheumatologic departments was drawn. At SIV and UNN, all eligible patients from the pediatric department were included. At St. Olav's, all eligible patients from all departments were included.

Assessments of medical records were performed by medical doctors highly experienced with the diagnosis and follow-up of patients with JIA (SVH, MR, EN, and SA). The children were categorized either as patients with JIA (true positives) or patients without JIA (false positives). The number of ICD-10 codes of M08/and or M09 in categories (1, ≥2, or ≥3) registered between January 1, 2008, and December 31, 2022, and JIA (yes or no) were registered for each patient.

Main exposure. We divided our study samples into three geographic areas from north to south based on the mother's region of living at the time of birth as given in the MBRN: the North, Mid, and South regions. Region South was used as the reference region.

Covariates in the MBRN sample. *Potential mediators.* To assess the effect of potential mediators on the association between region of birth and JIA, we included variables from different sources. From the MBRN we included maternal age, parity, mode of delivery, maternal smoking during pregnancy, child's sex, prematurity, season of birth, year of birth, and birth weight. Both education and income are measures used for an individual's socioeconomic status.[24] From SSB we categorized maternal educational level by October 1, 2020, into three groups (low, medium, and high). If the educational level was missing (n = 286,560), the household income from SSB was categorized into three groups (<25th percentile, 25th–75th percentile, or >75th percentile) and used instead. Because the frequency of antibiotic use is known to vary across regions in Norway and early antibiotic exposure is a potential risk factor for JIA,[25–27] we included information on systemic antibiotics given in the neonatal period from the MBRN and antibiotics dispensed from a pharmacy within age 2 years from NorPD.

JIA medication. To characterize the cases, we included data from NorPD on disease-modifying antirheumatic drugs (DMARDs) dispensed from a pharmacy to the cases between 2004 and 2021. These drugs were divided into two groups: methotrexate (MTX) and other DMARDs, including abatacept, tofacitinib, baricitinib, etanercept, adalimumab, certolizumab, golimumab, anakinra, tocilizumab, canakinumab, and secukinumab.

Genetic factors in the MoBa sample. In MoBa, blood samples were obtained from children (umbilical cord) at birth. DNA was extracted and stored at the NIPH.[28] The MoBa cohort genotyping was conducted through multiple research projects for several years.[29] A novel family-based pipeline (MoBaPsychGen genotype quality control [QC] pipeline) that includes preimputation QC, phasing, imputation, and postimputation QC was implemented to handle the complex relatedness structure of the cohort while taking into account the genotyping array and genotyping batch effects.[19]

We restricted the analysis to individuals of European ancestry selected based on a visual comparison of the first seven genetic principal components (PCs) with PCs from 1,000 genome phase 1 unrelated samples (n = 1,083), as described previously.[19] For each related pair in the study with individuals having a kinship coefficient >0.05, one member was excluded. The exclusion process gave priority to the retention of cases; all other exclusions were made randomly.

To assess each individual's genetic risk for JIA, we calculated polygenic risk scores (PRSs) from a genome-wide association study of JIA.[30] For this calculation, we used PRSice (version 2.3.5)[31] with various *P* value thresholds (5e–8, 1e–6, 1e–5, 1e–4, 1e–3, 1e–2, 5e–2, 1e–1, 5e–1, and 1). For further analyses, we extracted the first PCs of PRSs across all *P* value thresholds, following a widely applied method.[32] The genetic PCs were calculated as described in Corfield et al.[19]

Statistical analysis. In the validation of our case definition, we calculated the positive predictive values (PPVs) as the proportion of children with JIA, based on an assessment of medical records, out of all the children who were registered with at least one, two, or three M08 and/or M09 ICD-10 codes at each hospital. PPVs were calculated separately at each hospital and combined to obtain pooled results.

In the MBRN sample, we calculated the IR and cumulative incidence in all of Norway and separately for each of the three regions. To estimate the hazard ratio (HR) for JIA by geographic region, we used Cox regression. Additionally, we conducted Schoenfeld proportional hazards tests and log-log survival plots to assess whether the assumption of proportional hazards was

upheld. To assess the effect of potential mediators, we included perinatal factors, socioeconomic status, and systemic antibiotics during age 0 to 24 months in the adjusted Cox regression model.

In sensitivity analyses, we included maternal smoking during pregnancy. In further sensitivity analyses, we calculated the IR of JIA in different regions and the HR by region of birth with a stricter case definition. Additionally, we performed sensitivity analyses in which children born before 2007 were excluded because (1) the NPR contains individual-level data from 2008 and onward (allowing for the age at onset calculations)[23] and (2) JIA rarely manifests before age 1 year.[1]

To compare distributions of sex, medication use, and differences in the age of diagnosis for patients with JIA by region of birth in the MBRN sample (Supplementary Table 1), we used chi-square tests and Kruskal-Wallis test. To assess whether observed differences in the IR across geographic regions of Norway may be attributed to genetic differences, we ran logistic regression analyses in the MoBa sample. First, we tested the association between the region of birth and JIA (unadjusted model). In model 1, we included the covariates sex and year of birth. In model 2, we adjusted for sex, year of birth, and PRS for JIA. In model 3, we adjusted for sex, year of birth, PRS for JIA, and the first 10 genetic PCs. All statistical analyses were performed using STATA/SE V17 statistical software[33] and R (version 4.2.3).[34]

Ethics. The use of MBRN data with relevant linkages was approved by the Regional Committee for Medical and Health Research Ethics (REK #18622) and the Norwegian Data Protection Authority. The study was exempted from individual consent because it was a registry-based study with a low risk of personal identification. Involvement of patients and the public was considered not relevant in this study.

The validation study was approved by the Data Protection Officer (DPO) at each hospital for quality improvement purposes. Additionally, secondary approval was granted for the use of results in research projects. The current study with use of data from MoBaGenetics was approved by REK Southeast 28469 as part of the MoBaRheuma project. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The pregnant women provided written informed consent. The MoBa cohort is currently regulated by the Norwegian Health Registry Act.

RESULTS

Validation of case definition. In the validation, we included 1,086 children with at least one M08 or M09 code registered between 2008 and 2020. Out of these, 959 had at least two codes registered. In the validation, 913 patients with true JIA were identified. The PPV for those with at least two relevant ICD-10 codes was 93.4%. A less strict definition of only one code resulted in a PPV of 84.1% whereas a stricter definition of at least three relevant ICD-10 codes resulted in a PPV of 95.1% (Supplementary Table 2).

The MBRN sample. *Baseline characteristics by region of birth.* In the MBRN sample, we included 911,242 children and identified 1,184 patients with JIA after a median of 9.1 years (range 0.3–16.0 years) of follow-up (for flowchart, see Supplementary Figure 1). The distributions of baseline characteristics by region of birth are presented in Table 1. The maternal age was lower in regions North and Mid compared with region South, and the socioeconomic status and use of antibiotics during age 0 to 24 months was lower in region North compared with regions Mid and South.

Characteristics of patients with JIA. Among the patients, 796 (67.2%) were born in region South, 199 (16.8%) in region Mid, and 189 (16.0%) in region North (Figure 1). Of all patients, 746 (63.0%) were girls, and the median age of diagnosis was 5.0 years (range 0.3–16.0 years). The distribution of sex and age of diagnosis did not differ across the regions. The use of MTX and other DMARDs was lowest in region North (Supplementary Table 1).

Incidence of JIA by region of birth. The national cumulative incidence was 0.13% with 0.11% in region South, 0.16% in region Mid, and 0.24% in region North. In all of Norway, we found an IR per 100,000 PYs of 14.4 (95% confidence interval [CI] 13.6–15.2) (Figure 1). The IR increased gradually by latitude from 12.5 (95% CI 11.6–13.4) in region South to 25.9 (95% CI 22.5–29.9) in region North (Figure 1). Using region South as the reference category, the JIA in region North was HR = 2.07 (95% CI 1.77–2.43) and in region Mid it was HR = 1.43 (95% CI 1.23–1.67) (Table 2).

To study whether differences in the IR across regions were mediated by other recorded variables that differ across regions, we adjusted for all variables included in Table 1 in addition to birth year. With adjustments for perinatal factors, socioeconomic status, and systemic antibiotics during age 0 to 24 months when these factors were known (n = 902,379), the HR for JIA remained almost unchanged (Table 2). In further analyses when additionally adjusting for smoking during pregnancy when this was known (n = 733,980), the HR was essentially unchanged (Supplementary Table 3). In sensitivity analyses with a stricter case definition, the IR of JIA was slightly lower than with a case definition of at least two codes (Supplementary Table 4), but the HR comparing regions Mid and North with region South remained in magnitude (Supplementary Table 5). In further sensitivity analyses including children born from 2007 (n = 742,724), we found a numerically lower IR in all regions, and the HR for region North

Table 1. Baseline characteristics by region of birth in the Medical Birth Registry of Norway sample

	Region of birth		
	South (n = 708,943)	Mid (n = 122,910)	North (n = 79,389)
Maternal factors, n (%)			
Maternal age			
<25 years	95,270 (13.4)	21,449 (17.5)	17,440 (22.0)
25 to 34 years	469,214 (66.2)	80,489 (65.5)	47,943 (60.4)
≥35 years	144,458 (20.4)	20,972 (17.1)	14,006 (17.6)
Parity			
0	303,088 (42.8)	49,149 (40.0)	31,907 (40.2)
1	258,893 (36.5)	44,823 (36.5)	28,120 (35.4)
2	105,250 (14.9)	21,108 (17.2)	13,273 (16.7)
≥3	41,712 (5.9)	7,830 (6.4)	6,089 (7.7)
Mode of delivery			
Any Cesarean section[a]	117,514 (16.6)	21,265 (17.3)	13,098 (16.5)
Type of Cesarean section[a]			
Planned	44,720 (6.3)	7,635 (6.2)	4,615 (5.8)
Emergency	72,672 (10.3)	13,496 (11.0)	8,468 (10.7)
Not specified	122 (0.02)	134 (0.1)	15 (0.02)
Socioeconomic status[b]			
Low	131,499 (18.6)	20,678 (16.8)	16,142 (20.3)
Medium	234,171 (33.0)	45,153 (36.7)	28,845 (36.3)
High	339,275 (47.9)	56,695 (46.1)	34,020 (42.6)
Missing	3,998 (0.6)	384 (0.3)	382 (0.5)
Smoking through pregnancy			
No	525,430 (74.1)	97,875 (79.6)	57,326 (72.2)
Occasionally or changed	9,195 (1.3)	3,136 (2.6)	1,256 (1.6)
Yes	29,901 (4.2)	4,560 (3.7)	5,301 (6.7)
Missing	144,417 (20.4)	17,339 (14.1)	15,506 (19.5)
Child factors, n (%)			
Sex			
Female	344,663 (48.6)	59,920 (48.8)	38,725 (48.8)
Prematurity[c]			
Yes	45,062 (6.4)	7,276 (5.9)	4,758 (6.0)
Missing	3,774 (0.5)	297 (0.2)	193 (0.2)
Season of birth[d]			
Winter	164,210 (23.2)	28,246 (23.0)	18,690 (23.5)
Spring	183,673 (25.9)	31,731 (25.8)	20,324 (25.6)
Summer	191,148 (27.0)	33,430 (27.2)	21,116 (26.6)
Autumn	169,912 (24.0)	29,503 (24.0)	19,259 (24.3)
Birth weight, g			
<2,500	33,417 (4.7)	5,051 (4.1)	3,448 (4.3)
2,500 to 3,499	304,771 (43.0)	49,780 (40.5)	33,077 (41.7)
3,500 to 4,499	348,633 (49.2)	63,549 (51.7)	40,068 (50.5)
≥4,500	22,122 (3.1)	4,530 (3.7)	2,796 (3.5)
Antibiotic exposure during age 0 to 24 months			
Yes	294,268 (41.5)	49,978 (40.7)	26,303 (33.1)

[a] Vaginal birth was the reference category.
[b] Socioeconomic status was defined by the maternal educational level by October 1, 2020, categorized into three groups (low, medium, and high). If the educational level was missing (n = 286,560), the household income from Statistics Norway was used instead and categorized into three groups (<25th percentile, 25th–75th percentile, or >75th percentile).
[c] Gestational age <37 weeks.
[d] Winter was December to February, spring was March to May, summer was June to August, and autumn was September to November. There was one missing value for maternal age. There were no missing values for parity, mode of delivery, sex, birth weight, or antibiotic exposure during age 0 to 24 months.

compared with region South was slightly attenuated (Supplementary Tables 6 and 7).

Genetic factors in the MoBa sample by region of birth. From MoBa, we included 57,630 children and identified 238 patients with JIA (for flowchart, see Supplementary Figure 2). In unadjusted analyses, and when adjusting for sex and birth year, the risk of JIA was significantly higher in region North (odds ratio [OR] = 1.76, 95% CI 1.14–2.71; $P = 0.01$) compared with region South (Figure 2 and Table 3, model 1). When additionally adjusting for PRS in model 2, we observed an attenuation of association for region North (OR = 1.63, 95% CI 1.05–2.52; $P = 0.03$) and an

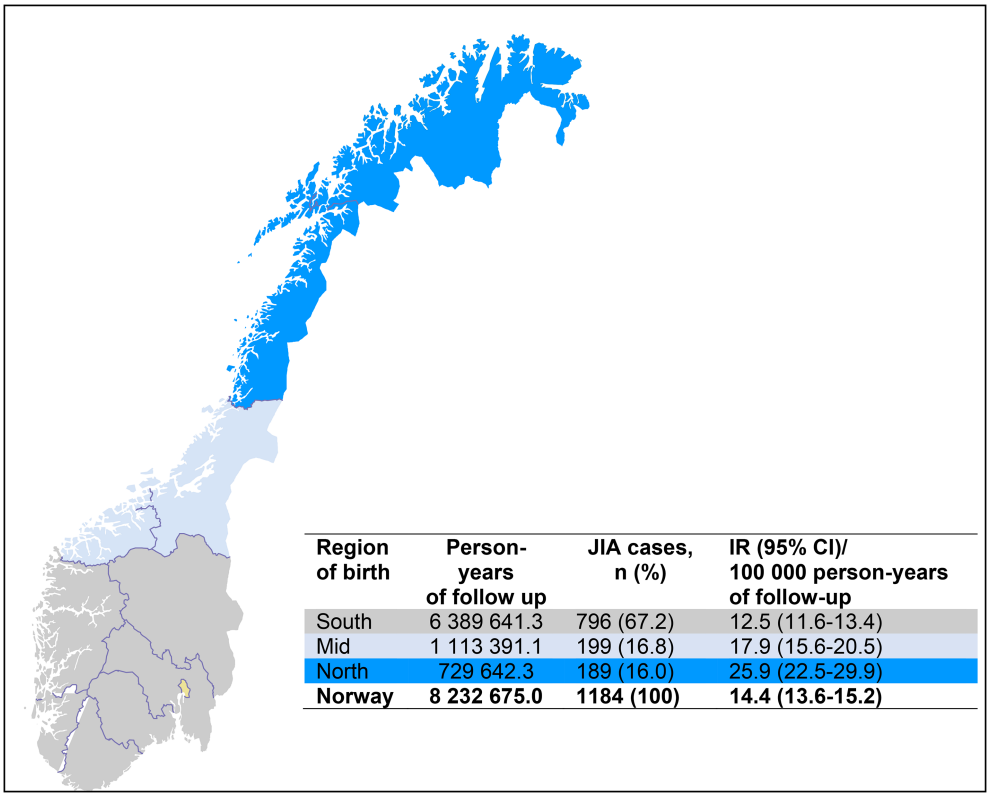

Figure 1. IR of JIA by region of birth in the Medical Birth Registry of Norway sample. CI, confidence interval; IR, incidence rate; JIA, juvenile idiopathic arthritis.

association between JIA diagnosis and PRS for JIA (OR = 1.79, 95% CI 1.57–2.03; *P* = 4.70e–19). When we further adjusted for the first 10 PCs (model 3), the association for region North became nonsignificant (OR = 1.29, 95% CI 0.73–2.27; *P* = 0.38), whereas we observed associations between JIA diagnosis and both PRSs for JIA (OR = 1.77, 95% CI 1.56–2.02; *P* = 2.77e–18) and the third genetic PC (OR = 8.53e–06, 95% CI 1.56e–09 to 0.05; *P* = 0.01).

DISCUSSION

In this nationwide study from Norway, we found an IR for JIA of 14.4/100,000 PYs with an increasing IR by increasing latitude. Adjustments for environmental factors such as perinatal factors, socioeconomic status, antibiotic use, and smoking did not substantially impact the results. In MoBa, the observed association between JIA and region of birth was no longer significant when adjusting for genetic factors.

The estimated national incidence is in line with previous studies from the Nordic countries and southeast of Norway reporting IRs of 15.0 and 14.0/100,000 PYs, respectively.[13,15] The national estimate in our study was quite close to these previous findings and is likely explained by a high proportion (78%) of the children in Norway residing in region South.

We were able to apply the same method across all regions, which makes a direct comparison of the regions feasible. Our findings support the existence of a north-south gradient, which may also exist outside of Norway. This is supported by previous

Table 2. HR for JIA by region of birth in the Medical Birth Registry of Norway sample*

Region	JIA, n (%)		HR unadjusted (95% CI)	HR adjusted (95% CI)[a]
	Yes (n = 1,184)	No (n = 940,571)		
South	796 (67.2)	708,147 (77.8)	Ref	Ref
Mid	199 (16.8)	122,711 (13.5)	1.43 (1.23–1.67)	1.42 (1.21–1.65)
North	189 (16.0)	79,200 (8.7)	2.07 (1.77–2.43)	2.11 (1.80–2.48)

* CI, confidence interval; HR, hazard ratio; JIA, juvenile idiopathic arthritis; Ref, reference.
[a] Adjusted for maternal age, parity, socioeconomic status, mode of delivery, prematurity, birth weight, systemic antibiotics during age 0 to 24 months, sex, year of birth, and season of birth. A total of 8,863 children were excluded because of missing covariate exposures.

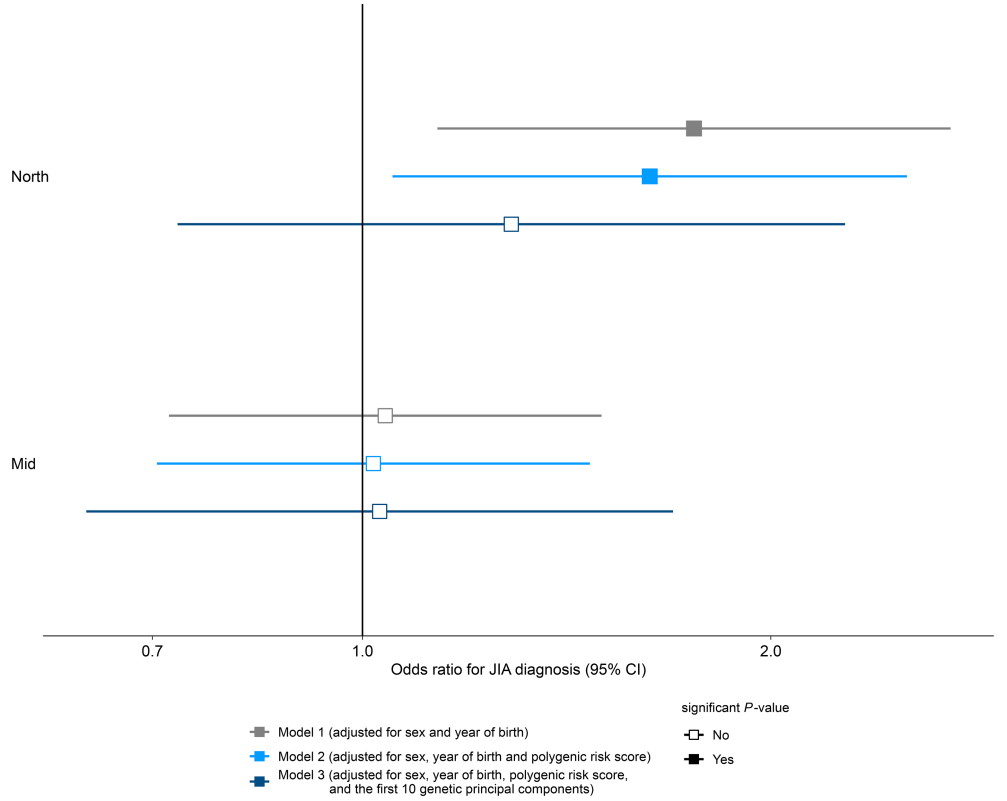

Figure 2. Associations between region of birth and JIA in the Norwegian Mother, Father, and Child Cohort Study sample. CI, confidence interval; JIA, juvenile idiopathic arthritis.

studies conducted in Nordic countries with a high IR, such as in Finland and Northern Norway,[13] compared with countries in Southern Europe, such as France and Spain, which have reported IRs in the range of 1.6 (95% CI 1.0–2.5) to 6.9 (95% CI 5.8–8.1). These rates are substantially lower compared with those observed in Nordic countries.[3,13–15] A previous study from northern parts of Norway also reported a high IR for JIA of 23.0/100,000 PYs.[14,15]

Interestingly, a recent study from the United Kingdom reported higher rates of JIA in the northern region of the United Kingdom compared with the southern regions.[35] Similarly, regional differences were also reported in Germany with a higher incidence in the north/northeast compared with the south/southwest.[36]

The existence of a north-south gradient in the incidence may indicate differences in environmental risk factors across regions.[7] We adjusted for perinatal factors, socioeconomic status, and antibiotic exposure during age 0 to 24 months as potential mediators, but we were not able to explain the observed north-south gradient by these factors.

A north-south gradient may also be caused by different genetic risk for JIA in different regions. In the MoBa sample, we found a higher occurrence of JIA in region North versus South (as observed in the MBRN sample) but no significant difference between regions Mid and South as opposed to the MBRN sample. This difference might be explained by selection bias[37,38] or insufficient power in the MoBa sample. When we adjusted for

Table 3. OR for JIA by region of birth in the Norwegian Mother, Father and Child Cohort Study sample with adjustments for genetic risk*

Region of birth	JIA, n		OR unadjusted (95% CI)	Model 1, OR adjusted (95% CI)[a]	Model 2, OR adjusted (95% CI)[b]	Model 3, OR adjusted (95% CI)[c]
	Yes (n = 238)	No (n = 57,392)				
South	181	45,854	Ref	Ref	Ref	Ref
Mid	34	8,284	1.04 (0.72–1.50)	1.04 (0.72–1.50)	1.02 (0.70–1.47)	1.03 (0.63–1.69)
North	23	3,254	1.79 (1.16–2.77)[d]	1.76 (1.14–2.71)[d]	1.63 (1.05–2.52)[d]	1.29 (0.73–2.27)

* CI, confidence interval; JIA, juvenile idiopathic arthritis; OR, odds ratio; Ref, reference.
[a] Adjusted for sex and year of birth.
[b] Adjusted for sex, year of birth, and polygenic risk score.
[c] Adjusted for sex, year of birth, polygenic risk score, and the first 10 genetic principal components.
[d] *P* value <0.05.

PRS, the observed association between region North and JIA was weakened. When further including the 10 genetic PCs, the association was no longer significant.

Taken together, our findings may indicate that genetic factors explain some of the regional differences, but other factors not examined in our study cannot be excluded. The first 10 genetic PCs represent a coarse-grained genetic background reflecting broad genetic ancestry and population admixtures. The observed association of JIA with genetic PCs might indicate higher genetic susceptibility to JIA in populations with certain genetic backgrounds or may be attributed to environmental risk factors for JIA, which are more common in certain populations but were not included in our study. These unknown underlying factors might be combinations of other environmental factors like vitamin D levels, air pollution, environmental toxicants, and infectious agents. Also, there may be interplay between genetic and environmental factors, which we have not investigated. Nonbiologic factors like health care–seeking behavior, health care services availability, or diagnostic accuracy across regions should be completely ruled out before confirming a true geographic difference. However, our validation data do not support these explanations.

A strength in our study is the public health care system and nationwide registers in Norway. We had access to prospectively collected data from population-based registers of high quality encompassing all regions with a virtually complete nationwide sample. This provided us with reliable data and the ability to make a direct comparison of rates in different regions.

Another strength was the ability to validate our outcome definition and to investigate possible regional differences in coding practices. Further, we included both relevant environmental factors and data on genetic risk as possible explanatory variables for the regional differences.

One limitation was that the age of diagnosis in the MBRN dataset was estimated by the year of first registration in the NPR and not accurately recorded. For children diagnosed before 2008, the year of their first registration was not available. Sensitivity analyses excluding children born before 2007 showed slightly lower IR in all regions and a slightly attenuated but still highly significant north-south gradient.

Because we only included children born in Norway, we had no data on children who immigrated during our study period. With a PPV of 93.4 in our case definition, approximately 7% of children might potentially be misclassified as having JIA. However, some milder cases may also not be captured if they do not seek medical care or receive a correct diagnosis. In addition, the highest PPV was found at UNN representing the northernmost region. A high PPV indicates a low risk of false positives, which underscores a true high IR in region North.

A stricter case definition of at least three codes, which showed a PPV of 95.1% would decrease the risk of false positives but also increase the risk of losing some true cases.[39] In sensitivity analyses using the strict case definition, the number of patients with JIA went from 1,148 to 1,087, but the north-south gradient remained consistent in magnitude. In the validation, all departments at St. Olav's Hospital were included, whereas in the other hospitals only the rheumatologic (OUS) and the pediatric department (OUS, SIV, and UNN) were included. These differences occurred because of different approvals by the local DPO and may have influenced the validation.

Environmental and genetic risk factors may vary across JIA categories,[2] but we lacked information regarding the specific categories within our samples. Previous studies have reported a high risk of JIA in indigenous populations of North America, Australia, and New Zealand.[1] Most of Norway's indigenous Sami live in the northern regions,[40] but we had no information about Sami ancestry in our study.

We were not able to include all environmental and genetic factors in both of our partly overlapping study samples. Because only a relatively small number of children were genotyped, our sample from MoBa may not be representative of all Norwegian children, and the results may be limited by lack of power. Thus, these results should be interpreted with caution.

In this nationwide study from Norway, we found an increasing HR for JIA with increasing latitude. The limited environmental factors available in our study did not seem to explain the gradient, whereas differences in genetic background between regions may explain some of the geographic variation. Further risk factors for JIA, including gene-environmental interplay that might explain the observed north-south gradient, should be investigated.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Hestetun confirms that all authors have provided the final approval of the version to be published, and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/ Declaration of Helsinki requirements.

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