Effects of birth months on rheumatic diseases in South Korea: a nationwide case-control study

J. Lee[1], J.H. Kim[1], M.K. Chung[2], M.-S. Park[3], S.-K. Kwok[1], H.W. Yim[3], S.-H. Park[1], J.H. Ju[1]

[1]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea;
[2]Division of Rheumatology, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Republic of Korea;
[3]Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.

Abstract

Objective

Birth month/season impacts the development of certain diseases. However, the effect of birth month/season on the development of rheumatic diseases has not been thoroughly investigated. Thus, the objective of this study was to determine whether birth month/season might affect the development of rheumatic diseases.

Methods

Birth month patterns of patients with various rheumatic diseases were compared with those of the general population. The dataset included 17,247,458 individuals from the health insurance review and assessment service database of Korea.

Results

Among 24 rheumatic diseases, the development of Crohn's disease, ulcerative colitis (UC), rheumatoid arthritis, Sjögren's syndrome, polymyalgia rheumatica, ankylosing spondylitis (AS), gout, and fibromyalgia (FM) was significantly associated with birth month/season. UC and AS were more prevalent in individuals born in February/winter. On the contrary, those who were born in June or July/summer were at a higher risk of gout and FM.

Conclusion

Seasonal variations in infectious agents, sun exposure, and food ingestion during gestation or early infancy seem to explain the association between birth month/season and development of rheumatic diseases.

Key words
seasonal variation, rheumatic diseases, epidemiology

Jennifer Lee, MD, PhD
Ji Hun Kim, MD
Min Kyung Chung, MD
Mi-Sun Park, MS
Seung-Ki Kwok, MD, PhD
Hyeon Woo Yim, MD, PhD
Sung-Hwan Park, MD, PhD
Ji Hyeon Ju, MD, PhD

Please address correspondence to:
Ji Hyeon Ju,
Division of Rheumatology,
Department of Internal Medicine,
College of Medicine,
Seoul St. Mary's Hospital,
The Catholic University of Korea,
222 Banpo-daero, Seocho-gu,
Seoul 06591, Republic of Korea.
E-mail: juji@catholic.ac.kr

Received on February 20, 2019;
accepted in revised form on July 1, 2019.

Funding: this study was supported by the Research Fund of Seoul St. Mary's Hospital, The Catholic University of Korea and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant no. HO16C0001).

Competing interests: none declared.

Introduction

It is believed that the time of a person's birth can affect his/her health outcome. The concept that birth month/season affects the development of certain diseases may have originated from myths surrounding the zodiac. However, it might have some scientific foundation. Cumulating evidence indicates that environmental factors encountered in early life, even at fetal stage, can have a marked impact on health in later life, including the risk of developing certain diseases (1-5). Because environmental factors such as temperature, sun exposure, and infectious agents are influenced by the month/season, birth month/season might be associated with disease development.

The pathogenesis underlying rheumatic diseases remains unclear. However, a common explanation is that rheumatic diseases develop when a 'genetically susceptible' individual encounters a relevant 'environmental trigger' (6-8). Therefore, one possible explanation is that environmental factors that vary according to month/season may induce epigenetic changes during gestational or neonatal period and subsequently contribute to the development of rheumatic diseases.

Several studies have demonstrated the impact of birth month/season on the risk of certain diseases, including asthma (9, 10), diabetes mellitus (11-16), multiple sclerosis (17), and thyroid disease (18). Although some studies have successfully demonstrated that birth month/season has a significant influence on disease development, results are inconsistent as different methods are used in various studies based on different populations. One underlying mechanism suggested by previous studies is the variability in levels of different types of virus or allergen according to season. For example, individuals born in the season when house dust mite is abundant are at higher risk of developing asthma later in life (19). More recently, Vitamin D has emerged as an important immune modulator (20). Vitamin D levels vary with sun exposure. Therefore, exposure during early life would be dependent on birth month/season. Indeed, Disanto *et al*. have investigated the association between birth month and immune-mediated diseases in the United Kingdom (21). They reported that six immune-mediated diseases [multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn's disease (CD), and ulcerative colitis (UC)] were more prevalent in those born in April but less so in those born in October. The authors argued that the risk of immune-mediated disease was inversely correlated with vitamin D status during the third trimester (21). Moreover, after examining 1,688 diseases using a dataset that included medical records of 1,749,400 individuals at New York Presbyterian/Columbia University Medical Center, 55 diseases were significantly affected by birth month (22).

Korea operates a single claim system, the Health Insurance Review and Assessment Service (HIRA) which covers nearly 90% of the population. Also, there is a special registration system that includes most patients with rheumatic diseases. This system verifies appropriate subject populations consisting of patients with proper diagnostic codes. Therefore, we used this information to examine whether birth month/season could affect the development of rheumatic diseases in a large unbiased study population.

Methods

Study population

Analyses were based on claims data from HIRA, including patient's diagnosis, treatment, procedures undergone, and drugs prescribed. The study population included patients whose claims were received by HIRA between January 1997 and August 2015. Diseases were classified according to the Korean standard classification of diseases (KCD) 6, a modified Korean version of the International classification of diseases (ICD)-10 generated by the Ministry of Korea Health and Welfare. Access to raw data of HIRA service is regulated by the Rules for Data Exploration and Utilization of the HIRA. Researchers who want to access HIRA data should submit a study proposal to HIRA and obtain approval for data use from the data access com-

Table I. Estimated peak-to-low ratio and 95% CI for the month of birth.

	Low month		Peak month		Peak-to-low PLR (95% CI)	*p*-value
	month	%	month	%		
Overall						
Crohn's disease	3	0.101	11	0.126	1.243 (1.161-1.330)	<0.001
Ulcerative colitis	4	0.247	2	0.269	1.090 (1.007-1.140)	<0.001
Rheumatoid arthritis	6	0.639	3	0.675	1.057 (1.023-1.088)	<0.001
Sjögren's syndrome	11	0.094	2	0.105	1.119 (0.934-1.203)	0.003
Polymyalgia rheumatica	11	0.027	5	0.034	1.244 (1.049-1.427)	0.002
Ankylosing spondylitis	3	0.233	2	0.267	2.347 (1.078-2.477)	<0.001
Gout	12	5.529	7	5.916	1.070 (1.040-1.081)	<0.001
Fibromyalgia	1	2.063	6	2.133	1.034 (1.022-1.051)	<0.001
Male						
Crohn's disease	3	0.140	11	0.176	1.263 (1.066-1.373)	<0.001
Ulcerative colitis	4	0.295	2	0.315	1.069 (1.046-1.135)	0.027
Rheumatoid arthritis	7	0.261	9	0.285	1.093 (1.020-1.168)	0.009
Sjögren's syndrome	12	0.018	1	0.022	1.172 (1.034-1.472)	0.171
Polymyalgia rheumatica	2	0.017	3	0.022	1.314 (1.127-1.646)	0.017
Ankylosing spondylitis	3	0.365	2	0.414	1.133 (1.100-1.192)	<0.001
Gout	12	9.394	7	9.881	1.052 (1.032-1.064)	<0.001
Fibromyalgia	9	1.459	6	1.535	1.052 (1.022-1.083)	0.001
Female						
Crohn's disease	3	0.068	10	0.081	1.194 (1.066-1.336)	0.002
Ulcerative colitis	4	0.203	2	0.227	1.118 (1.046-1.196)	0.001
Rheumatoid arthritis	6	0.982	7	1.037	1.056 (1.020-1.093)	0.002
Sjögren's syndrome	11	0.162	7	0.181	1.122 (1.034-1.218)	0.006
Polymyalgia rheumatica	11	0.035	5	0.047	1.329 (1.127-1.568)	0.001
Ankylosing spondylitis	8	0.113	2	0.136	1.202 (1.100-1.313)	<0.001
Gout	12	2.076	6	2.193	1.056 (1.032-1.081)	<0.001
Fibromyalgia	12	2.581	6	2.692	1.043 (1.022-1.065)	<0.001

mittee of HIRA (Big Data Division, Healthcare Data Convergence Department, HIRA, opendata@hira.or.kr). Request for data can be sent by accessing http://www.hira.or.kr/dummy.do?pgmid=HIRAA070001000430. Researchers cannot access personal information of subjects such as names or addresses. Only anonymous data are accessible.

Birth month patterns of patients with rheumatic diseases were compared with those of individuals without each disease. A total of 24 rheumatic diseases [sarcoidosis, CD, UC, RA, psoriatic arthritis, juvenile idiopathic arthritis, polyarteritis nodosa, microscopic polyangiitis, granulomatous polyangiitis, Takayasu's arteritis, giant cell arteritis, SLE, dermatomyositis, polymyositis, systemic sclerosis, Sjogren's syndrome (SS), mixed connective tissue disease, Behçet's disease, polymyalgia rheumatica (PMR), ankylosing spondylitis (AS), relapsing polychondritis, antiphospholipid syndrome, gout, and fibromyalgia (FM)] were selected. Eosinophilic granulomatous polyangiitis (a disease suffered by less than 100 patients) was excluded from the analysis. CD, UC, and sarcoidosis are commonly associated with rheumatic diseases. Thus, they were included for analysis. For each disease, frequency of patients with the disease of a specific birth month/season was calculated. The risk of certain birth month/ season for certain disease was then estimated. Patients whose birth months were not collected or appeared to be incorrect (values other than 1–12 or two or more inconsistent birth months) were excluded. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, Seoul, South Korea (approval no.: KC15RISI0685).

Definitions

Subjects were classified as having a certain disease using the major diagnosis (the diagnosis that came first) code entered. In Korea, most rheumatic diseases are classified as rare and intractable diseases that are registered and managed separately by the government. Therefore, diagnostic codes for rare and intractable diseases are given only when a diagnosis is clear. For this reason, individuals with a minor diagnosis code were also regarded as having the disease. Subject was classified as having the disease when his/her claim was received at least once during the study period. Spring season included March, April, and May. Summer season covered June, July, and August. Fall season included September, October, and November. Winter season included December, January, and February.

Statistical analysis

The significance of unimodal cyclic pattern in the proportion of rheumatic diseases cases was tested by Walter and Elwood's method and a cosinor model that took variations in population at-risk into account. The Walter-Elwood test is a parametric test for seasonality that uses a simple harmonic curve and allows for a variable population at risk (23). The cosinor analysis is a common approach that describes data by a single cosine function with fixed frequency plus a constant (single-harmonic model), yielding three parameters: amplitude, phase, and mean (24). To represent the magnitude of seasonal ef-

Table II. Simple logistic regression for the month of birth.

	Overall				Male				Female			
	non-event	event	crude OR(95% CI)	*p*-value	non-event	event	crude OR(95% CI)	*p*-value	non-event	event	crude OR(95% CI)	*p*-value
Crohn's disease												
rest	15920000	1310088			7580516	630764			8336793	679324		
	(92.4)	(7.6)			(92.32)	(7.68)			(92.47)	(7.53)		
highest month	18410	1651	1.090	0.001	12277	1113	1.090	0.006	6133	538	1.077	0.101
	(91.77)	(8.23)	(1.036-1.146)		(91.69)	(8.31)	(1.025-1.159)		(91.94)	(8.06)	(0.986-1.176)	
Ulcerative colitis												
rest	15540000	1664203			7415753	783866			8123149	880337		
	(90.33)	(9.67)			(90.44)	(9.56)			(90.22)	(9.78)		
highest month	39867	4486	1.051	0.002	22571	2480	1.040	0.063	17296	2006	1.070	0.004
	(89.89)	(10.11)	(1.019-1.084)		(90.1)	(9.9)	(0.998-1.084)		(89.61)	(10.39)	(1.022-1.121)	
Rheumatoid arthritis												
rest	15460000	1670492			7422959	779168			8040877	891324		
	(90.25)	(9.75)			(90.5)	(9.5)			(90.02)	(9.98)		
highest month	101771	11359	1.034	0.001	20344	2199	1.030	0.187	81427	9160	1.015	0.181
	(89.96)	(10.04)	(1.014-1.054)		(90.25)	(9.75)	(0.986-1.077)		(89.89)	(10.11)	(0.993-1.037)	
Sjögren's syndrome												
rest	15560000	1666936			7436845	786192			8126223	880744		
	(90.33)	(9.67)			(90.44)	(9.56)			(90.22)	(9.78)		
highest month	15701	1753	1.043	0.094	1479	154	0.985	0.859	14222	1599	1.038	0.159
	(89.96)	(10.04)	(0.993-1.096)		(90.57)	(9.43)	(0.834-1.163)		(89.89)	(10.11)	(0.986-1.093)	
Polymyalgia rheumatica												
rest	15850000	1395841			7560897	662120			8285449	733721		
	(91.9)	(8.1)			(91.95)	(8.05)			(91.86)	(8.14)		
highest month	4797	474	1.122	0.017	1522	131	0.983	0.851	3275	343	1.183	0.003
	(91.01)	(8.99)	(1.021-1.233)		(92.08)	(7.92)	(0.822-1.175)		(90.52)	(9.48)	(1.058-1.322)	
Ankylosing spondylitis												
rest	15540000	1664236			7409301	783093			8130450	881143		
	(90.33)	(9.67)			(90.44)	(9.56)			(90.22)	(9.78)		
highest month	39018	4453	1.066	<0.0001	29023	3253	1.060	0.002	9995	1200	1.108	0.001
	(89.76)	(10.24)	(1.033-1.099)		(89.92)	(10.08)	(1.023-1.100)		(89.28)	(10.72)	(1.043-1.176)	
Gout												
rest	15070000	1200352			6881344	557006			8187498	643346		
	(92.62)	(7.38)			(92.51)	(7.49)			(92.71)	(7.29)		
highest month	902781	75483	1.050	<0.0001	725250	61070	1.041	<0.0001	177531	14413	1.034	0.000
	(92.28)	(7.72)	(1.042-1.058)		(92.23)	(7.77)	(1.032-1.050)		(92.49)	(7.51)	(1.016-1.052)	
Fibromyalgia												
rest	15730000	1153361			7541151	560724			8192992	592637		
	(93.2)	(6.8)			(93.08)	(6.92)			(93.25)	(6.75)		
highest month	334822	25132	1.024	0.000	114055	8740	1.031	0.006	220767	16392	1.027	0.001
	(93.0)	(7.0)	(1.011-1.038)		(92.88)	(7.12)	(1.009-1.054)		(93.09)	(6.91)	(1.010-1.043)	

fects, the peak-to-low ratio was derived from the peak and the nadir of the sine curve fitted through seasonality data. In addition, binary logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals (CI) for seasonal and monthly impact on rheumatic diseases. ORs of the peak were estimated for seasonal models with the rest other than peak as a reference. Statistical analyses were performed in R language v. 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) using the package season. Statistical significance was set at $p<0.05$.

Results

Characteristics of the study population

A total of 17,247,458 subjects (8,224,670 males and 9,022,788 females) were included. Age distribution of the study population is described in Supplementary Table S1. Most of the study subjects aged 46–50 and 51–55 years, representing 11.76% and 12.70% of the cohort, respectively. The number of subjects born in each month is shown in Supplementary Table S2. The number of subjects born in winter was greater than that born in other seasons, consistent with Korean birth reports from the Korean statistical information service.

Birth month/season is associated with the development of rheumatic diseases

Birth month showed a significant association with the development of 8 rheumatic diseases (CD, UC, RA, SS, PMR, AS, gout, and FM) among 24 rheumatic diseases evaluated (Suppl. Table S3). When stratified with gender, only gout and fibromyalgia were significantly affected by birth month in male popula-

Table III. Summary of trend and seasonality tests for season of birth.

						Cosinor tests	
	Spring	Summer	Fall	Winter	Amplitude	cos (*p*-value)	sin (*p*-value)
Overall	n=4464793	n=3852747	n=4091001	n=4838917			
Crohn's disease	4858 (0.109)	4565 (0.118)	4908 (0.120)	5730 (0.118)	2489	<0.001	0.001
Ulcerative colitis	11131 (0.249)	9826 (0.255)	10675 (0.261)	12721 (0.263)	9810.15	<0.001	<0.001
Rheumatoid arthritis	29669 (0.665)	25042 (0.650)	26642 (0.651)	31777 (0.657)	32623.74	<0.001	<0.001
Sjögren's syndrome	4627 (0.104)	3918 (0.102)	3977 (0.097)	4932 (0.102)	6242.15	<0.001	<0.001
Polymyalgia rheumatica	1467 (0.033)	1227 (0.032)	1163 (0.028)	1414 (0.029)	1751.89	<0.001	<0.001
Ankylosing spondylitis	10989 (0.246)	9534 (0.247)	10325 (0.252)	12623 (0.261)	12670.27	<0.001	<0.001
Gout	250375 (5.608)	225506 (5.853)	230127 (5.625)	272256 (5.626)	174814.12	<0.001	<0.001
Fibromyalgia	93232 (2.088)	81210 (2.108)	85021 (2.078)	100491 (2.077)	80316.97	<0.001	<0.001
Male	n=2098288	n=1859527	n=1965298	n=2301557			
Crohn's disease	3172 (0.151)	3090 (0.166)	3271 (0.166)	3857 (0.168)	1397.98	<0.001	0.083
Ulcerative colitis	6255 (0.298)	5610 (0.302)	6054 (0.308)	7132 (0.310)	4591.2	<0.001	<0.001
Rheumatoid arthritis	5834 (0.278)	4964 (0.267)	5418 (0.276)	6327 (0.275)	5401.76	<0.001	<0.001
Sjögren's syndrome	420 (0.020)	363 (0.020)	391 (0.020)	459 (0.020)	367.65	0.006	0.045
Polymyalgia rheumatica	446 (0.021)	385 (0.021)	379 (0.019)	443 (0.019)	353.77	0.023	0.017
Ankylosing spondylitis	8085 (0.385)	7202 (0.387)	7647 (0.389)	9342 (0.406)	7999.95	<0.001	<0.001
Gout	199660 (9.515)	182207 (9.799)	185645 (9.446)	218808 (9.507)	124398.35	<0.001	<0.001
Fibromyalgia	31220 (1.488)	28006 (1.506)	29293 (1.491)	34276 (1.489)	20942.52	<0.001	<0.001
Female	n=2366505	n=1993220	n=2125703	n=2537360			
Crohn's disease	1686 (0.071)	1475 (0.074)	1637 (0.077)	1873 (0.074)	1156.1	<0.001	0.002
Ulcerativecolitis	4876 (0.206)	4216 (0.212)	4621 (0.217)	5589 (0.220)	5357.51	<0.001	<0.001
Rheumatoid arthritis	23835 (1.007)	20078 (1.007)	21224 (0.998)	25450 (1.003)	27313.6	<0.001	<0.001
Sjögren's syndrome	4207 (0.178)	3555 (0.178)	3586 (0.169)	4473 (0.176)	5915.57	<0.001	<0.001
Polymyalgia rheumatica	1021 (0.043)	842 (0.042)	784 (0.037)	971 (0.038)	1443.03	<0.001	<0.001
Ankylosing spondylitis	2904 (0.123)	2332 (0.117)	2678 (0.126)	3281 (0.129)	5014.59	<0.001	<0.001
Gout	50715 (2.143)	43299 (2.172)	44482 (2.093)	53448 (2.106)	53834.98	<0.001	<0.001
Fibromyalgia	62012 (2.620)	53204 (2.669)	55728 (2.622)	66215 (2.610)	59693.84	<0.001	<0.001

Table IV. Estimated peak-to-low ratio and 95% CI for the season of birth.

	Low season		Peak season		Peak-to-low PLR (95% CI)	*p*-value
	season	%	season	%		
Overall						
Crohn's disease	spring	0.109	fall	0.120	1.103 (1.060-1.147)	<0.001
Ulcerative colitis	spring	0.249	winter	0.263	1.054 (1.028-1.082)	<0.001
Rheumatoid arthritis	summer	0.650	spring	0.665	1.022 (1.005-1.040)	0.01
Sjögren's syndrome	fall	0.097	spring	0.104	1.066 (1.022-1.112)	0.003
Polymyalgia rheumatica	fall	0.028	spring	0.033	1.156 (1.070-1.248)	<0.001
Ankylosing spondylitis	spring	0.246	winter	0.261	1.060 (1.033-1.087)	<0.001
Gout	spring	5.608	summer	5.853	1.044 (1.038-1.050)	<0.001
Fibromyalgia	winter	2.077	summer	2.108	1.015 (1.006-1.024)	0.002
Male						
Crohn's disease	spring	0.151	winter	0.168	1.109 (1.058-1.162)	<0.001
Ulcerative colitis	spring	0.298	winter	0.310	1.040 (1.005-1.075)	0.025
Rheumatoid arthritis	summer	0.267	spring	0.278	1.042 (1.003-1.082)	0.035
Sjögren's syndrome	summer	0.020	spring	0.020	1.025 (0.891-1.180)	0.727
Polymyalgia rheumatica	winter	0.019	spring	0.021	1.104 (0.968-1.259)	0.139
Ankylosing spondylitis	spring	0.385	winter	0.406	1.053 (1.023-1.085)	0.001
Gout	fall	9.446	summer	9.799	1.037 (1.031-1.044)	<0.001
Fibromyalgia	spring	1.488	summer	1.506	1.012 (0.996-1.029)	0.14
Female						
Crohn's disease	spring	0.071	fall	0.077	1.081 (1.010-1.157)	0.025
Ulcerative colitis	spring	0.206	winter	0.220	1.069 (1.029-1.111)	0.001
Rheumatoid arthritis	fall	0.998	summer	1.007	1.009 (0.990-1.029)	0.369
Sjögren's syndrome	fall	0.169	summer	0.178	1.057 (1.009-1.107)	0.019
Polymyalgia rheumatica	fall	0.037	spring	0.043	1.170 (1.066-1.284)	0.001
Ankylosing spondylitis	summer	0.117	winter	0.129	1.105 (1.048-1.165)	<0.001
Gout	fall	2.093	summer	2.172	1.038 (1.024-1.052)	<0.001
Fibromyalgia	winter	2.610	summer	2.669	1.024 (1.013-1.036)	<0.001

tion. On the other hand, seasonal birth effects remained significant in female population except for CD and RA. In terms of peak to low ratio (PLR), all except male SS (10% of female SS) were significantly affected by birth month (Table I). However, when the highest month was compared with the rest of months using simple logistic regression analysis, only AS, gout, and FM remained significant regardless of gender (Table II).

Birth season was also significantly associated with the risk of all 8 diseases shown by cosinor test (Table III). PLR was significant in CD, UC, AS, and gout (Table IV). Comparison with the highest and others showed seasonal impact in AS and gout (Table V).

Interestingly, UC and AS showed the lowest prevalence in individuals born in March and the highest prevalence in those born in February (Fig. 1). Consistently, when seasonal impacts were evaluated, individuals had the lowest risk for UC and AS if they were born in spring but had the highest risk if

Table V. Simple logistic regression for the season of birth.

	Overall				Male				Female			
	non-event	event	crude OR(95% CI)	*p*-value	non-event	event	crude OR(95% CI)	*p*-value	non-event	event	crude OR(95% CI)	*p*-value
Crohn's disease												
rest	13140000 (76.28)	4086093 (23.72)			5913580 (72.02)	2297700 (27.98)			6892051 (76.44)	2124066 (23.56)		
highest season	15153 (75.53)	4908 (24.47)	1.042 (1.009-1.076)	0.012	9533 (71.19)	3857 (28.81)	1.042 (1.003-1.081)	0.033	5034 (75.46)	1637 (24.54)	1.055 (0.998-1.116)	0.059
Ulcerative colitis												
rest	12380000 (71.95)	4826196 (28.05)			5905194 (72.02)	2294425 (27.98)			6471715 (71.88)	2531771 (28.12)		
highest season	31632 (71.32)	12721 (28.68)	1.032 (1.011-1.053)	0.003	17919 (71.53)	7132 (28.47)	1.025 (0.997-1.053)	0.084	13713 (71.04)	5589 (28.96)	1.042 (1.010-1.075)	0.009
Rheumatoid arthritis												
rest	12700000 (74.12)	4435124 (25.88)			6109673 (74.49)	2092454 (25.51)			6959059 (77.91)	1973142 (22.09)		
highest season	83461 (73.77)	29669 (26.23)	1.018 (1.005-1.032)	0.009	16709 (74.12)	5834 (25.88)	1.020 (0.990-1.050)	0.203	70509 (77.84)	20078 (22.16)	1.004 (0.989-1.020)	0.592
Sjögren's syndrome												
rest	12770000 (74.11)	4460166 (25.89)			6125169 (74.49)	2097868 (25.51)			7017302 (77.91)	1989665 (22.09)		
highest season	12827 (73.49)	4627 (26.51)	1.033 (0.999-1.068)	0.058	1213 (74.28)	420 (25.72)	1.011 (0.905-1.130)	0.847	12266 (77.53)	3555 (22.47)	1.022 (0.985-1.061)	0.247
Polymyalgia rheumatica												
rest	12780000 (74.11)	4463326 (25.89)			6125175 (74.49)	2097842 (25.51)			6653686 (73.77)	2365484 (26.23)		
highest season	3804 (72.17)	1467 (27.83)	1.104 (1.040-1.173)	0.001	1207 (73.02)	446 (26.98)	1.079 (0.968-1.203)	0.171	2597 (71.78)	1021 (28.22)	1.106 (1.029-1.189)	0.007
Ankylosing spondylitis												
rest	12380000 (71.95)	4826294 (28.05)			5900179 (72.02)	2292215 (27.98)			6477514 (71.88)	2534079 (28.12)		
highest season	30848 (70.96)	12623 (29.04)	1.049 (1.028-1.071)	<0.0001	22934 (71.06)	9342 (28.94)	1.049 (1.024-1.074)	0.000	7914 70.69)	3281 (29.31)	1.060 (1.017-1.104)	0.005
Gout												
rest	12640000 (77.7)	3627241 (22.3)			5761030 (77.45)	1677320 (22.55)			6880923 (77.92)	1949921 (22.08)		
highest season	752758 (76.95)	225506 (23.05)	1.044 (1.039-1.049)	<0.0001	604113 (76.83)	182207 (23.17)	1.036 (1.031-1.042)	<0.0001	148645 (77.44)	43299 (22.56)	1.028 (1.017-1.039)	<0.0001
Fibromyalgia												
rest	13120000 (77.67)	3771537 (22.33)			6270354 (77.39)	1831521 (22.61)			6845613 (77.92)	1940016 (22.08)		
highest season	278744 (77.44)	81210 (22.56)	1.013 (1.005-1.021)	0.001	94789 (77.19)	28006 (22.81)	1.012 (0.998-1.025)	0.094	183955 (77.57)	53204 (22.43)	1.021 (1.011-1.031)	<0.0001

they were born in winter (Fig. 2). Gout showed the most marked birth month pattern: the prevalence peaked in December, with a trough in June. This condition was also impacted by the season, showing a peak in winter and a trough in summer. In addition, females born in summer were more likely to suffer from fibromyalgia and PMR. The risk of RA was the highest for individuals born in March and the lowest for those born in June. However, the seasonal impact was not significant when stratified by gender.

Discussion

Here, we used nationwide Korean data and found that birth month/season had a significant effect on the development of certain rheumatic diseases. Although this association does not prove causality or explain the underlying mechanism, this result is meaningful in that this is the first study to examine the association between birth month and the development of various rheumatic diseases in a large population.

Birth season impacted the development of AS and UC. Both AS and UC showed low prevalence in people born in spring. However, they showed high prevalence in people born in winter. To the best of our knowledge, this is the first time an association between birth month and development of AS is reported. Several studies have examined the relationship between seasonality and inflammatory bowel disease (IBD) in different areas of the world, although their methods were different to ours. However, results of these studies on IBD were inconsistent due to differences in ethnicity and geographic area in

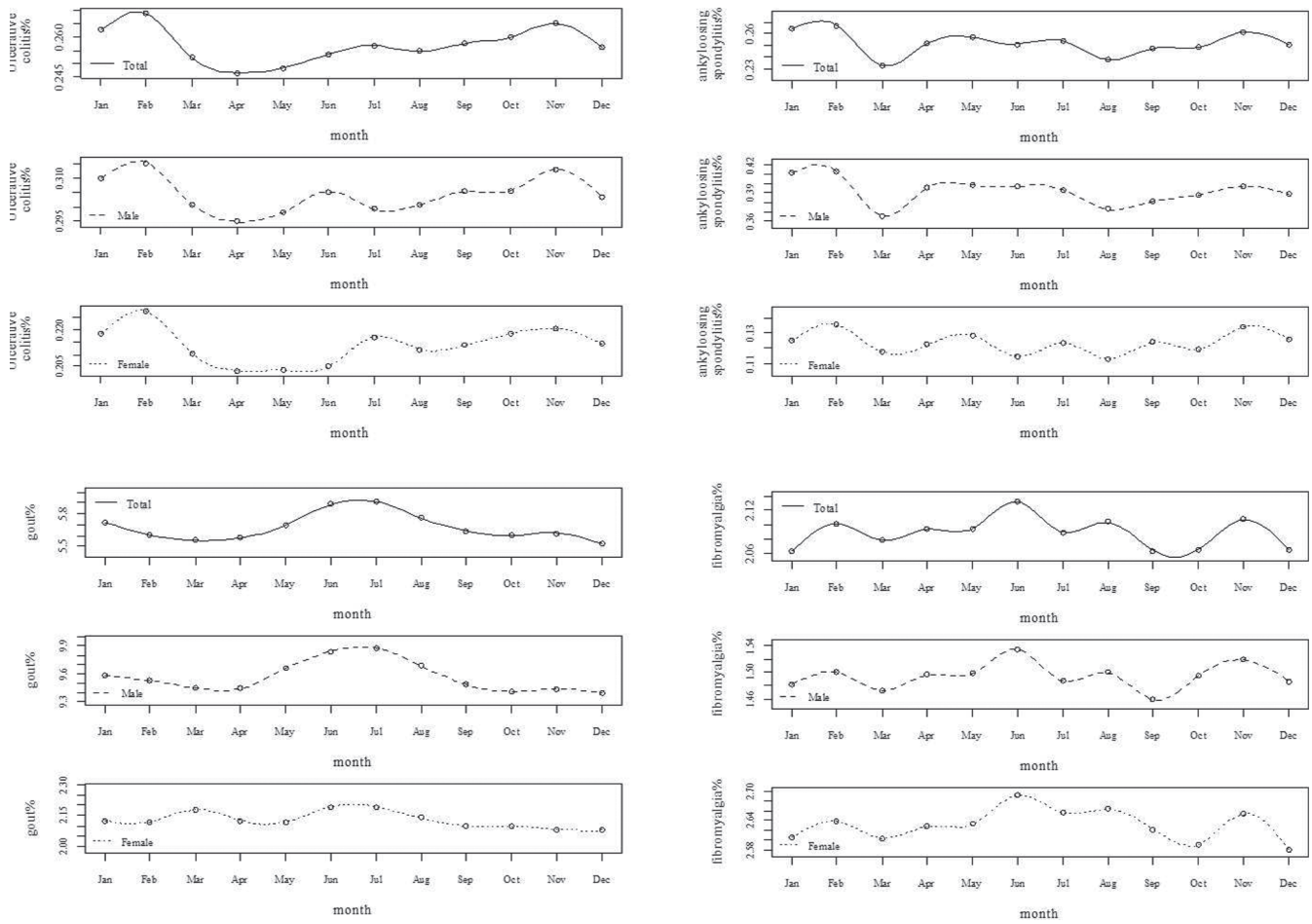

Fig 1. Ancillary analysis of the ratio of the number of patients with certain diseases over the total and gender-stratified population born in each month.

which they were conducted. One study conducted in Canada found a high risk for people born in April (25) whereas another study in China found a low risk for people born in spring/summer (26). A study from the UK found no association between birth month and IBD (27). By contrast, a study conducted in Korea did find an association between birth month and IBD (28) after examining 411 patients with UC and 316 patients with CD, all recruited from six university hospitals. The study found that those born during the winter had an increased risk of IBD, particularly UC (28), consistent with results of the present study. In the present study, AS and UC showed a similar pattern. This is interesting because these diseases have several common features that can classify them within the spectrum of spondylitis. The consistent impact of birth season may suggest a common pathogenetic mechanism, albeit one that is yet to be identified.

In addition, this is also the first study to demonstrate an association between birth month and gout. The birth month pattern was the most dramatic of all diseases examined, peaking in June with a trough in December. Seasonal impact was also apparent, peaking in summer with the lowest in winter. Again, there is no clear explanation for this. Future studies should elucidate the mechanism underlying the impact of birth month/season on gout.

The risk of RA was also affected significantly by birth month. A study of patients with musculoskeletal diseases attending a rehabilitation center in Norway conducted in 1987 found that twice as many patients born in summer suffered problems than those born in winter (29). However, in the same year, a Canadian study revealed that birth month had no significant effect on the development of RA among 910 patients (30). Since then, conflicting results about the effect of birth month on RA have been reported (31). Here, we found that the risk of RA was high for individuals born in March but low for those born in June.

Although some studies have demonstrated an association between birth month/season and disease, the exact mechanisms are unclear. Differences in results might be due to exposure to environmental agents such as viruses, sun exposure, and temperature *in utero* or during early infancy. These factors all could induce epigenetic changes. It is well known that rheumatic disease develops when a genetically susceptible individual encounters environmental triggers. Some triggers may be determined early in life. Indeed, babies who are frequently exposed to high sugar levels *in utero* are more likely to develop type 2 diabetes as adults, suggesting an environmental effect.

Seasonal variation in serum vitamin D level has been suggested to play a role in seasonal birth effects. Disanto *et al*.

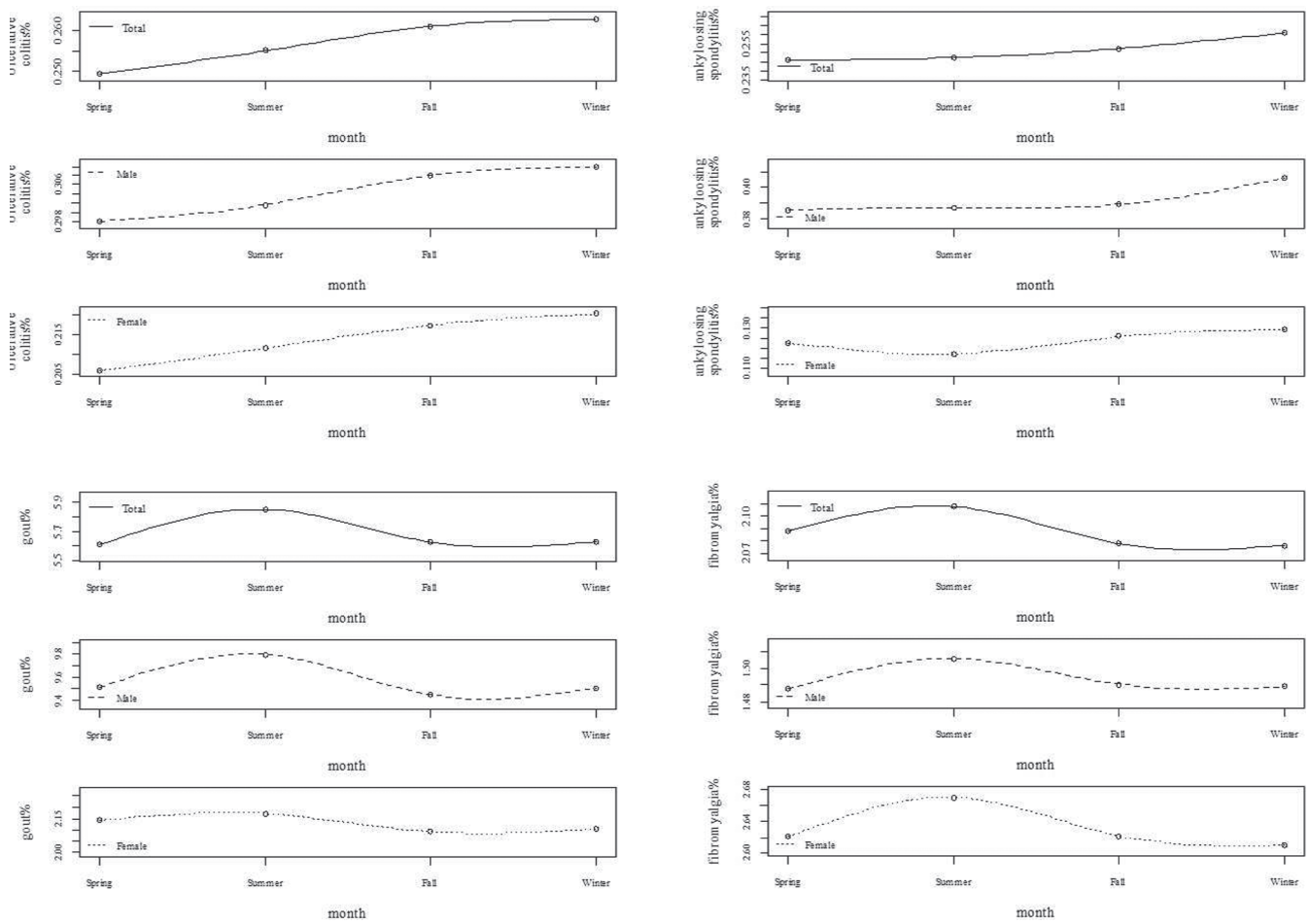

Fig 2. Ancillary analysis of the ratio of the number of patients with certain disease over the total and gender-stratified population born in each season.

(21) have suggested that vitamin D levels are affected by birth month/season. Due to its immune modulating effect, vitamin D deficiency during the second trimester may play an important role in disease development. However, there is controversy over the role of vitamin D as well. Thorsen *et al*. (32) have reported no association between vitamin D levels around the time of birth and the risk of developing juvenile idiopathic arthritis in later life. Unfortunately, we could not investigate vitamin D levels in the present study population, making it impossible to prove/disprove the hypothesis. Considering that differences in vitamin D levels between seasons in areas that lie at high latitude are high, it would be intriguing to examine whether there is a difference in birth month pattern for the same disease between regions with low seasonal variation and those with high seasonal variation.

The present study has several limitations. First, it was retrospective in nature and data were obtained from a claims database. Therefore, we could not match clinical manifestations with laboratory findings. Indeed, even within the same disease, there exist different genetic and pathogenic backgrounds. Therefore, analysis of the disease as one may result in some misinterpretation. However, Korea has a single claim system that covers the vast majority of people in Korea. In addition, the number of study subjects was large enough to avoid errors or bias. Moreover, the diagnosis of rare/intractable diseases appeared to be accurate because doctors reported the evidence on which they based their diagnoses at the time they registered patients. Therefore, it is highly likely that the diagnosis code in our study population is correct, particularly in cases of rare/intractable disease. Second, this is a cross sectional study. Therefore, we cannot prove causality. Moreover, although we found that birth month/season had a statistically significant impact on the risk of developing rheumatic disease, its contribution appeared trivial because most of odds ratios did not exceed 1.5. However, this is unsurprising given that the pathogenesis of autoimmune diseases is complex and multifactorial. Third, we could not adjust for potential confounding factors such as birth year and region. However, the change in latitude is small according to the region in Korea. In addition, we performed gender-stratified analysis to reduce confounding effects in this study.

In conclusion, birth month/season has a significant impact on the development of certain rheumatic diseases in the Korean population. Seasonal variations in levels of infectious agents, sun exposure, and food ingestion during gestation or early infancy may explain this association. Future investigations should examine whether this is associated with epigenetic modifications that predispose individuals to disease development.

References

1. ZHANG GQ, LIU B, LI J *et al*.: Fish intake during pregnancy or infancy and allergic outcomes in children: a systematic review and meta-analysis. *Pediatr Allergy Immunol* 2017; 28: 152-61.
2. WARSTEDT K, FURUHJELM C, FALTH-MAGNUSSON K, FAGERAS M, DUCHEN K: High levels of omega-3 fatty acids in milk from omega-3 fatty acid-supplemented mothers are related to less immunoglobulin E-associated disease in infancy. *Acta Paediatr* 2016; 105: 1337-47.
3. RUSS K, HOWARD S: Developmental exposure to environmental chemicals and metabolic changes in children. *Curr Probl Pediatr Adolesc Health Care* 2016; 46: 255-85.
4. LOGAN KM, EMSLEY RJ, JEFFRIES S *et al*.: Development of early adiposity in infants of mothers with gestational diabetes mellitus. *Diabetes Care* 2016; 39: 1045-51.
5. DALEY D: The evolution of the hygiene hypothesis: the role of early-life exposures to viruses and microbes and their relationship to asthma and allergic diseases. *Curr Opin Allergy Clin Immunol* 2014; 14: 390-6.
6. SMOLEN JS, ALETAHA D, MCINNES IB: Rheumatoid arthritis. *Lancet* 2016.
7. LONG H, YIN H, WANG L, GERSHWIN ME, LU Q: The critical role of epigenetics in systemic lupus erythematosus and autoimmunity. *J Autoimmun* 2016; 74: 118-38.
8. FOX RI: Sjögren's syndrome. *Lancet* 2005; 366: 321-31.
9. SAITOH Y, DAKE Y, SHIMAZU S *et al*.: Month of birth, atopic disease, and atopic sensitization. *J Investig Allergol Clin Immunol* 2001; 11: 183-7.
10. CHANG WC, YANG KD, WU MT *et al*.: Close correlation between season of birth and the prevalence of bronchial asthma in a Taiwanese population. *PLoS One* 2013; 8: e80285.
11. KORDONOURI O, SHUGA N, LEWY H, ASHKENAZI I, LARON Z: Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in Berlin differs from the general population. *Eur J Pediatr* 2002; 161: 291-2.
12. WILLIS JA, SCOTT RS, DARLOW BA, LEWY H, ASHKENAZI I, LARON Z: Seasonality of birth and onset of clinical disease in children and adolescents (0-19 years) with type 1 diabetes mellitus in Canterbury, New Zealand. *J Pediatr Endocrinol Metab* 2002; 15: 645-7.
13. GROVER V, LIPTON RB, SCLOVE SL: Seasonality of month of birth among African American children with diabetes mellitus in the city of Chicago. *J Pediatr Endocrinol Metab* 2004; 17: 289-96.
14. VAISERMAN AM, CARSTENSEN B, VOITENKO VP *et al*.: Seasonality of birth in children and young adults (0-29 years) with type 1 diabetes in Ukraine. *Diabetologia* 2007; 50: 32-5.
15. LEWY H, HAMPE CS, KORDONOURI O *et al*.: Seasonality of month of birth differs between type 1 diabetes patients with pronounced beta-cell autoimmunity and individuals with lesser or no beta-cell autoimmunity. *Pediatr Diabetes* 2008; 9: 46-52.
16. KAHN HS, MORGAN TM, CASE LD *et al*.: Association of type 1 diabetes with month of birth among U.S. youth: The SEARCH for Diabetes in Youth Study. *Diabetes Care* 2009; 32: 2010-5.
17. DOBSON R, GIOVANNONI G, RAMAGOPALAN S: The month of birth effect in multiple sclerosis: systematic review, meta-analysis and effect of latitude. *J Neurol Neurosurg Psychiatry* 2013; 84: 427-32.
18. KRASSAS GE, TZIOMALOS K, PONTIKIDES N, LEWY H, LARON Z: Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differ from that in the general population. *Eur J Endocrinol* 2007; 156: 631-6.
19. KORSGAARD J, DAHL R: Sensitivity to house dust mite and grass pollen in adults. Influence of the month of birth. *Clin Allergy* 1983; 13: 529-35.
20. DALL'ARA F, CUTOLO M, ANDREOLI L, TINCANI A, PAOLINO S: Vitamin D and systemic lupus erythematous: a review of immunological and clinical aspects. *Clin Exp Rheumatol* 2018; 36: 153-62.
21. DISANTO G, CHAPLIN G, MORAHAN JM *et al*.: Month of birth, vitamin D and risk of immune-mediated disease: a case control study. *BMC Med* 2012; 10: 69.
22. BOLAND MR, SHAHN Z, MADIGAN D, HRIPCSAK G, TATONETTI NP: Birth month affects lifetime disease risk: a phenome-wide method. *J Am Med Inform Assoc* 2015; 22: 1042-53.
23. WALTER SD, ELWOOD JM: A test for seasonality of events with a variable population at risk. *Br J Prev Soc Med* 1975; 29: 18-21.
24. NELSON W, TONG YL, LEE JK, HALBERG F: Methods for cosinor-rhythmometry. *Chronobiologia* 1979; 6: 305-23.
25. SHAW SY, NUGENT Z, TARGOWNIK LE, SINGH H, BLANCHARD JF, BERNSTEIN CN: Association between spring season of birth and Crohn's disease. *Clin Gastroenterol Hepatol* 2014; 12: 277-82.
26. BAI A, GUO Y, SHEN Y, XIE Y, ZHU X, LU N: Seasonality in flares and months of births of patients with ulcerative colitis in a Chinese population. *Dig Dis Sci* 2009; 54: 1094-8.
27. SONNENBERG A: Date of birth in the occurrence of inflammatory bowel disease. *Inflamm Bowel Dis* 2009; 15: 206-11.
28. JUNG YS, SONG CS, KIM ER *et al*.: Seasonal variation in months of birth and symptom flares in Korean patients with inflammatory bowel disease. *Gut Liver* 2013; 7: 661-7.
29. FØNNEBO V: Month of birth and prevalence of misculoskeletal diseases later in life. *Lancet* 1987; 329: 739-40 (originally published as Volume 1, Issue 8535).
30. BUCHANAN WW, GREGOIRE LG, BUCHANAN HM: Month of birth and rheumatoid arthritis. *Lancet* 1988; 330: 517.
31. BERKUN Y, LEWY H, PADEH S, LARON Z: Seasonality of birth of patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2015; 33: 122-6.
32. THORSEN SU, PIPPER CB, ALBERDI-SAUGSTRUP M *et al*.: No association between vitamin D levels around time of birth and later risk of developing oligo- and polyarticular juvenile idiopathic arthritis: a Danish case-cohort study. *Scand J Rheumatol* 2016: 1-8.