





# Association of Arthritis Onset with Influenza: Analysis of the Canadian Early Inflammatory Arthritis Cohort

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**Objective.** To evaluate seasonal patterns of early inflammatory arthritis (IA) onset and potential associations with IA symptom onset.

**Methods.** The Canadian Early Arthritis Cohort (CATCH) is an inception cohort study of adults with early (12 months or less) IA. We used patient reports of symptom onset as a proxy of IA onset and examined the seasonal distribution of IA onset over 10 years. Influenza time series was based on laboratory-confirmed influenza A and B from the Canadian FluWatch surveillance from 2010–2016. Bivariate analysis of influenza and IA was performed using cross-correlations with different time lags and Poisson regression. IA and influenza were recorded as monthly total frequencies.

**Results.** Of 2519 IA patients, 88% had confirmed rheumatoid arthritis (RA). Significantly, more IA onsets occurred in winter compared with other seasons ( $P = 0.03$ ); although IA onset was more frequent in January, the difference between months was not statistically significant. Compared to months with the lowest influenza rates, months with the highest influenza rates had a statistically significant, but trivial, increase of 0.003% in the incidence of IA (incidence rate ratio (95% confidence interval): 1.00003 (1.00005; 1.000053),  $P = 0.02$ ).

**Conclusion.** Although IA symptom onset occurs more frequently in winter, we found that flu outbreaks were not associated with a meaningful increase in IA symptom onset in a large, well-characterized cohort of Canadian adults over 6 years.

## INTRODUCTION

Early inflammatory arthritis (IA) is a recent-onset arthropathy that may resolve spontaneously, develop into rheumatoid arthritis (RA), another definite arthropathy, or remain undifferentiated (1). RA is the most common IA worldwide, with 0.5%–1% prevalence and annual incidence of 25–55 cases per 100,000 population (2–4).

RA is an autoimmune disease perturbation (5,6). The role of viral infections as potential environmental triggers of autoimmune diseases such as RA has been widely discussed (7,8). Our recent

meta-analysis showed that parvovirus B19 and chronic hepatitis C infections are associated with the development of RA and that chikungunya virus is associated with the development of persistent IA (9).

Influenza is a common viral infection worldwide with usual annual epidemics during the late fall through early spring (10). Influenza has been linked to the development of autoimmune disorders (11–14), but its effect on the risk of developing IA/RA is poorly understood. A significant association was found between rheumatoid factor (RF)-positivity and the presence of anti-influenza antibodies after an epidemic of influenza A in 1957 (odds ratio

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## SIGNIFICANCE & INNOVATIONS

- RA has seasonal timing of onset.
- This corresponds with the timing of influenza.
- However, the association is implied but very weak (yet statistically significant enough) when adjusting for other known risk factors.

[95% confidence interval (CI)] = 13.6 [1.4; 127.4],  $P = 0.02$ (15). Influenza was also accompanied by high levels of human leucocyte antigen D-related expression on monocytes, which is an indicator for antigen-presentation ability and T-cell activation. Others have shown a significant increase in interleukin-1, interleukin-6, and tumor necrosis factor- $\alpha$  levels in response to influenza stimuli (16). Thus, the similarities of the cytokines and cells involved in the pathogenesis of influenza and RA, coupled with the presence of RF+ in adults with RA years before its overt clinical manifestation (17–19), offer a potential mechanism through which exposure to the influenza virus may trigger development of RA.

The aim of the study was to examine seasonal patterns of IA symptom onset and its relation to influenza outbreaks, including different lags (ie, induction periods) between exposure and outcome epochs.

## METHODS

Study methods and results are reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology Guidelines (20).

**Study design.** Data from a multisite inception cohort of patients with early IA suspected to be RA (Canadian Early Arthritis Cohort [CATCH]) were analyzed and combined with data from the Canadian national flu surveillance program (<https://www.canada.ca/en/services/health/diseases-conditions.html>) to evaluate exposure-outcome relationships. The CATCH study has ethics approval obtained from each participating CATCH site, and patients signed informed consent.

**Setting and Study Population.** *Inflammatory arthritis.* Participants were adults with early IA recruited from 19 sites across Canada from January 2007 through January 2017. Within CATCH, RA is diagnosed using 1987 ACR or 2010 ACR/EULAR criteria, but patients are not required to meet these criteria at enrollment (3,21). Diagnosis of IA is confirmed by a rheumatologist, with the majority (88%) meeting RA classification criteria. Patients with infectious, crystal-induced, psoriatic arthritis or other connective tissue diseases at baseline or subsequent to enrollment (22) were excluded. Patients from CATCH receive treatment according to the discretion of the treating rheumatologist and in accordance with the Canadian guidelines for RA management (23,24).

*Influenza.* In September 2010, the Public Health Agency of Canada launched a national surveillance program (FluWatch) to monitor influenza and influenza-like illnesses across Canada. FluWatch identifies influenza cases by reviewing hospital, laboratory, and admission databases and infection control logs for patients hospitalized during influenza season with a documented positive influenza test (<https://www.canada.ca/en/services/health/diseases-conditions.html>).

**Measures.** *Primary Outcome.* The main outcome was the total monthly cases of IA symptom onset based on patient reports from CATCH across all participating sites. IA onset is often insidious, and there are often several months of delay before the patient is diagnosed by a physician (25). At enrollment, patients were asked, “When did you have your first episode of joint pain and swelling lasting for at least 6 weeks?” Physician-reported IA symptom onset was recorded by rheumatologists based on patient reports of the first episode of joint pain and swelling lasting longer than 6 weeks. All patients enrolled in CATCH could have had IA symptoms for up to 12 months prior to enrollment. IA onset was recorded as month/year.

*Exposure variable.* Regional reports of influenza diagnoses were the exposure of interest. We used laboratory-confirmed new influenza A and B cases from September 1 2010 to December 30 2016 in each province from the FluWatch database. Influenza time series was recorded as monthly total frequencies through the same time period. It is important to note that this was not a study of confirmed influenza in people developing early RA/suspected RA but was a correlation of the timing of RA onset and the background rate of influenza cases over each month, with data of 6 years superimposed.

**Sociodemographic variables.** Patient age, sex, ethnicity, education, and smoking status were obtained from a sociodemographic questionnaire.

**Confounders.** Because the main unit of analysis was the month of disease onset (and not individuals), common risk factors (eg, age, sex, education) that do not change from month to month were not included.

**Statistical analysis.** Baseline descriptive statistics were calculated and characteristics between patients with confirmed RA vs. undifferentiated IA were compared using independent  $t$  tests and  $\chi^2$ . The number of IA and influenza onset cases was recorded as the monthly cumulative values. All results were reported at a two-sided level of significance of 0.05.

Median monthly IA onset was aggregated over a 10-year period from January 2006 to January 2016 and presented graphically using box plots. One-way analysis of variance was used to compare differences in symptom onset across the 12 months of a year. Potential seasonal variations in aggregate IA

onset across winter (December–February) vs. all other seasons were compared using two-sample *t* test.

The association between monthly influenza and IA onset from September 2010 to December 2016 inclusively was assessed using cross-correlations (26). The cross-correlation method is based on identifying lags of the input series *x* at time *t* (influenza) that can be predictive of the response series *y* at time *t* (IA). A maximum number of 12 lags for influenza (1 lag = 1 month based on our data) that might be predictive of IA were included, with zero lag representing cross-correlation of IA with influenza onset during the same month. As we were interested in whether influenza leads to chronic IA (suspected or proven RA), we reported correlation coefficients only for negative lags. We investigated whether short-term variation in the IA onset can be partially explained by changes in the influenza onset over time using Poisson regression for count data. Time series Poisson regression analysis (27) (with adjusted standard errors to account for overdispersion) was used to examine incidence rate ratio (IRR) after adjustment for seasonality and long-term trends that might obscure the true exposure-outcome relationship. By definition, IRR is a ratio of two incidence rates in exposed and unexposed individuals. In the context of our study that uses a month as the main unit of analysis, months with the highest influenza activity were considered as exposed months, and months with the lowest influenza activity were considered as unexposed months. Statistical analysis was performed using SAS 9.4 software (28) and Stata SE 13 software (29).

Physician and patient symptom onset dates were compared using intraclass correlation coefficients (ICCs) (30) and were categorized into three levels based on agreement (31). We pre-specified the minimum ICC with at least moderate reliability (ICC = 0.60–0.74) to use patient-reported date of symptom onset to measure IA onset over time.

## RESULTS

**Sample characteristics at study entry.** At the time of data extraction (12 October 2017), 2519 patients constituted the final sample of patients with less than 13 months of symptoms at enrollment. Among them, 88% (*n* = 2209) fulfilled RA classification criteria. Patients' characteristics at study entry are provided in Table 1. The majority of IA patients were female (71%), white (82%), had more than a high school education (58%), and were current/past smokers (56%), with a mean (SD) age of 55 (15) years and mean (SD) symptom duration of 5 (3). Baseline disease activity based on Disease Activity Score 28 (DAS28)–C-reactive protein (CRP) three-variable and DAS28–Erythrocyte Sedimentation Rate (ESR) three-variable was  $4.6 \pm 1.3$  and  $4.9 \pm 1.5$ , respectively. Patients with IA had mean  $\pm$  SD ESR of  $27 \pm 23$  mm/h, CRP of  $14 \pm 18$  mg/l, Health Assessment Questionnaire Disease activity score of  $1.0 \pm 0.7$ , and were RF- and Anti-citrullinated protein antibody

**Table 1.** Sample characteristics at study entry

Characteristics	All IA Cohort ( <i>n</i> = 2519)
<b>Sociodemographic characteristics</b>	
Age, mean (SD), years	55 (15)
Female, <i>n</i> (%)	1791 (71)
Caucasian ethnicity, <i>n</i> (%)	2053 (82)
Education $\leq$ high school, <i>n</i> (%)	1051 (42)
Never smoked, <i>n</i> (%)	1109 (44)
<b>Disease characteristics at baseline</b>	
Patient-reported symptom duration mean (SD), months (from baseline visit)	5 (3)
Physician-reported symptom duration mean (SD), months (from baseline visit)	5 (3)
Tender 28 joint count, mean (SD)	8 (7)
Swollen 28 joint count, mean (SD)	7 (6)
DAS28 (CRP) three-variable, mean (SD)	4.6 (1.3)
DAS28 (ESR) three-variable, mean (SD)	4.9 (1.5)
ESR, mean (SD), mm/h	27 (23)
CRP, mean (SD), mg/l	14 (18)
HAQ DI, mean (SD)	1.0 (0.7)
RF positive,* <i>n</i> (%)	1103 (44)
ACPA positive,* <i>n</i> (%)	958 (53)

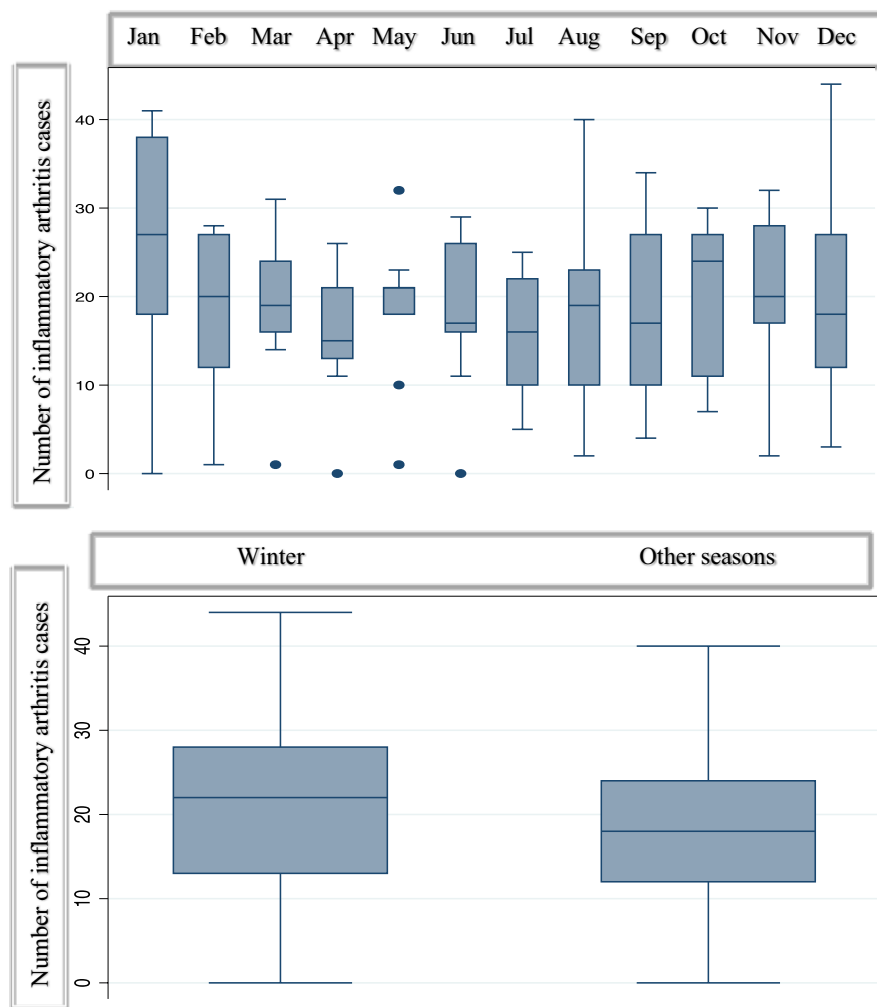
Abbreviation: RA, rheumatoid arthritis; UIA, undifferentiated inflammatory arthritis; DAS, disease activity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ DI, Health Assessment Questionnaire Disease activity; RF, rheumatoid factor; ACPA, antibodies against citrullinated proteins.

\* Missing data affected the number of subjects for these variables.

(ACPA)-positive in 44% and 53% of cases, respectively. However, there were *n* = 12 (0.5%) missing data for RF status and *n* = 702 (28%) for ACPA status.

**Univariate analysis of inflammatory arthritis time series.** We visually assessed the number of IA onsets from the CATCH cohort by month and season (Figure 1) and quantitatively assessed for the entire study period. The number of IA symptom onset for 10-year aggregated data varied; the highest being in January, but the overall differences between months were not statistically significant (Figure 1, top panel; *P* = 0.6). There were significantly more IA onsets in winter than in other seasons (mean 22 (95% CI (18; 25)) and 18 (95% CI (17; 20)), respectively, *P* = 0.03) (Figure 1, bottom panel).

**Bivariate time series analysis of inflammatory arthritis and influenza.** Figure 2 shows plots of the IA and influenza time series over six years. IA symptom onset tended to have noticeable peaks in January and troughs in summer, with, however, the exception of August 2014. The downward trend at the end of the study period reflects an artifact of decreased enrollment in CATCH, not in incidence. Cross-correlations between new influenza and IA symptom onset are presented in Figure 3.



**Figure 1.** Inflammatory arthritis onset aggregated by month (top panel) and aggregated by season (bottom panel), 2006-2016.

As you can see from the figure, all the correlation coefficients on the y axis are clustered around the null value (ie, zero).

As there was moderate agreement between patient- and physician-reported symptom month of onset (ICC (95% CI) = 0.70 (0.67; 0.79), we used patient reports of onset for the time series calculations.

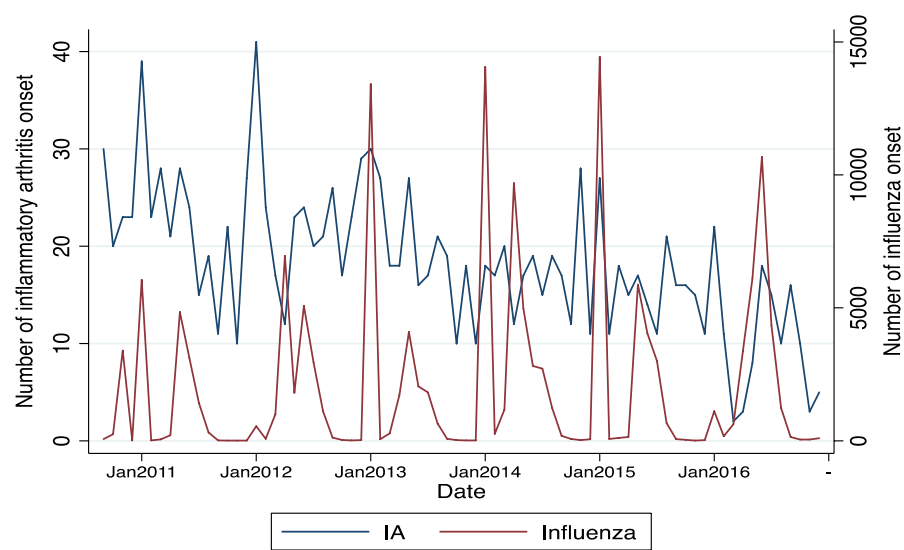
Time series regression analyses, which are unadjusted for seasonal and long-term patterns, may risk spurious conclusions. Therefore, we applied the flexible spline function of time fitted to the IA time series to remove these patterns from our data. As we can see in Figure 4, the model with splines does not reveal any seasonal pattern over time. Adjusted for seasonality and long-term trend regression of IA on influenza, time series estimated that, compared with months that had the lowest influenza rates, months with the highest influenza rates had a statistically significant but trivial increase of 0.003% in the incidence of IA (IRR [95% CI] 1.00003 [1.000005; 1.000053],  $P = 0.02$ ). No effect of influenza on IA onset was evident when IA onset was lagged by 1 and 3 months (0.99 [95% CI (0.99; 1.00),  $P = 0.84$ ], and 0.99 [95% CI (0.99; 1.00),  $P = 0.33$ ], respectively).

## DISCUSSION

There are few studies that evaluate seasonal variability of IA/RA. Our time series analysis is, to our knowledge, the first to assess the monthly and seasonal distribution of early-incident IA onsets over 10 years of observation. We found that in a large incident cohort of Canadians with IA, significantly more reported onset in winter compared with other seasons.

Jacoby, Jayson, and Cosh also reported that in Bath, United Kingdom, more RA onset occurred in winter, with December being the highest onset month (32). Söderlin et al observed that in Swedish RA patients observed in 1996-2004, symptom onset was most likely to occur from December through March as compared with other months (33). Silman et al found inconsistent peaks of incident IA in the United Kingdom in April and October over 2 years of observations (34).

Similarly, when we examined IA symptom onset and influenza by month over 6 years, we observed similar peaks of onset in January. Results from cross-correlation analysis showed random scattering of cross-correlations with no evidence of association

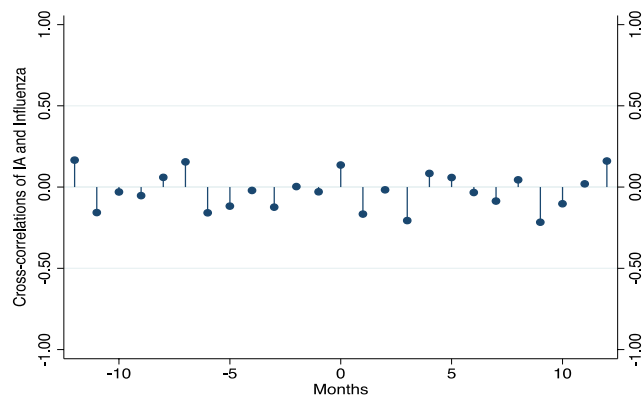


**Figure 2.** Time series of inflammatory arthritis and influenza onset over time, 2010-2016.

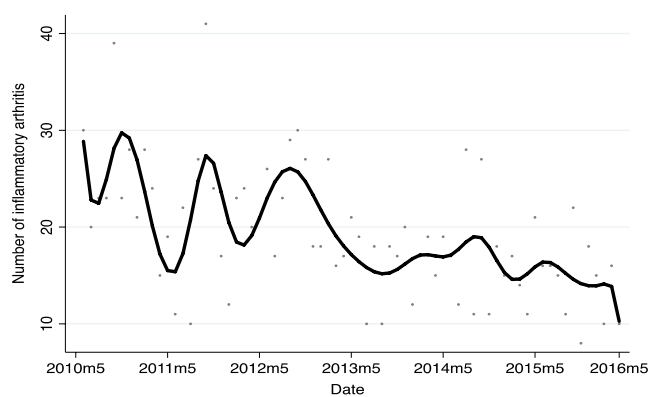
between IA and influenza. Furthermore, after adjusting for seasonal and long-term trends, the risk of IA that is due to influenza was trivial, only explaining 0.3% of IA per 100 cases of influenza.

Our study had several strengths. Our research is based on a large sample of patients with well-characterized IA inception cohort with patients drawn from 19 centers across Canada. Patient demographics in CATCH are similar to the population-based studies (4,35). Including patients with recent symptom-onset IA (12 months or less) helped to minimize the risk of recall bias. We minimized the risk of disease misclassification and reporting bias by using only laboratory-confirmed influenza A and B cases retrieved from the influenza surveillance program. We applied the time series regression analysis at the population level, at which traditional risk factors, such as age, sex, and health status, that do not significantly change from month to month are not necessary to include as confounders. Even though participation in CATCH is voluntary and not every incident IA case was captured in this cohort, the estimated IRR with months determining the exposed and unexposed groups was unlikely affected by study participation as the

rates of influenza were not determined by recall but by regional surveillance. Additionally, we did not prove that the patients in the CATCH cohort had influenza at similar rates as those in the regional provincial surveillance data. Our study also has limitations. First, there is a risk of ascertainment bias and underreporting of influenza cases. There might be additional confounding factors that were not measured. For example, low socioeconomic-status individuals may be predisposed to influenza and may also experience greater difficulty accessing care. Use of ecological data on influenza exposure preclude making causal inferences about influenza and IA onset in individuals. Because essentially, there was no association with timing of influenza, we did not subset patients with RA meeting criteria vs. those not meeting criteria, as all patients enrolled in the CATCH cohort are thought to have RA, and since the association was statistically significant but weak, the results would not change if we eliminated the 12% who did not meet ACR criteria for RA. Additionally, even if an association had been found, this would only be a study of correlations between onset of IA and onset of influenza from surveillance programs and



**Figure 3.** Cross-correlations of new inflammatory arthritis and influenza onsets, 2010-2016.



**Figure 4.** Trends in the inflammatory arthritis over time, 2010-2016 (flexible spline function).



would not have necessarily been a cause-and-effect relationship as influenza serology was not collected in this cohort.

In conclusion, we found that although early IA onset tends to cluster in winter months, we found no meaningful increase in IA onset that was due to influenza.

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## AUTHOR CONTRIBUTIONS

All authors were involved in the study design, data analysis, initial outlines, drafting, and final approval of the manuscript.

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