



Arthritis Care & Research

Vol. 71, No. 8, August 2019, pp 1084–1091 DOI 10.1002/acr.23743 © 2018, American College of Rheumatology

Trends in the Prevalence and Incidence of Psoriasis and Psoriatic Arthritis in Ontario, Canada: A Population-Based Study

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Objective. To estimate the prevalence and incidence of psoriasis and psoriatic arthritis (PsA) over time in Ontario, Canada.

Methods. We performed a population-based study of Ontario health administrative data, using validated case definitions for psoriasis and PsA. We computed the crude and age- and sex-standardized cumulative prevalence and incidence of psoriasis from 2000 to 2015.

Results. Among the 10,774,802 individuals ages ≥20 years residing in Ontario in 2015, we identified 273,238 patients with psoriasis and 18,655 patients with PsA, equating to cumulative prevalence estimates of 2.54% and 0.17%, respectively. Correcting the prevalence estimates for imperfect sensitivity and specificity resulted in similar estimates. The male:female ratio was approximately 1.0 for both conditions. For psoriasis, the age- and sex-standardized cumulative prevalence increased from 1.74% in 2000 to 2.32% in 2015. For PsA, the age- and sex-standardized cumulative prevalence increased from 0.09% in 2008 to 0.15% in 2015. Between 2008 and 2015, annual incidence rates for psoriasis decreased, whereas those for PsA remained relatively stable.

Conclusion. The prevalence and incidence of psoriasis and PsA in Ontario are similar to those observed in Europe and the US. The steady increase in the prevalence of psoriasis and PsA over the past decade may be due to a combination of population aging, population growth, and increasing life expectancy.

INTRODUCTION

Psoriasis is an immune-mediated chronic skin disease that may involve other organ systems, including the joints. Although generally not life-threatening, psoriasis may be associated with important morbidity and disability. It can range from a very mild disease with a few small plaques to severe widespread skin lesions that may lead to disability and poor quality of life (1). The impact of

moderate-to-severe disease on physical, mental, and emotional well-being is similar to that of other serious, chronic conditions, including diabetes mellitus and cancer (2,3). Furthermore, psoriasis is associated with other comorbidities that contribute to the burden of disease on quality of life, physical function, and survival (4,5). Up to one-third of the patients with psoriasis develop an inflammatory arthritis termed psoriatic arthritis (PsA) (6). In most patients, PsA runs a course of a chronic, progressive disease that

The opinions, results, and conclusions reported herein are those of the authors and are independent from the funding sources. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred. Parts of this material are based on data and/or information compiled and provided by the Canadian Institutes of Health Information, but the analyses, conclusions, opinions and statements expressed in the material are those of the authors and not necessarily those of Canadian Institutes of Health Information.

Supported by the International Psoriasis and Arthritis Team and the Canadian Rheumatology Association (Canadian Initiative for Outcomes in Rheumatology Care) and by the Institute for Clinical Evaluative Sciences, funded by the Ontario Ministry of Health and Long-Term Care. Dr. Eder's work was supported by a New Investigator Salary Award from the Arthritis Society. Dr. Tu's work was supported by a Research Scholar award from the Department of Family and Community Medicine at the University of Toronto.

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication May 7, 2018; accepted in revised form August 28, 2018.

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SIGNIFICANCE & INNOVATIONS

- The study provides real-world data that enhance our understanding of the epidemiology of psoriatic disease in a population of more than 10 million adult individuals.
- In 2015, the prevalence of psoriasis and psoriatic arthritis in Ontario was 2.54% and 0.17%, respectively.
- The cumulative prevalence of both PsA and psoriasis has gradually increased over the past decade, while at the same time global incidence rates of both have either remained stable or slightly decreased.
- The steady increase in the prevalence of psoriasis and PsA over the past decade may be due to a combination of population aging, population growth, and increasing life expectancy.

can lead to severe joint damage and disability that are comparable to those that occur in rheumatoid arthritis (7). Thus, PsA poses a major health burden, in addition to that caused by psoriasis alone.

The prevalence of psoriasis in population-based studies from Europe ranges from 1.3% to 8.5% (8). Data about the epidemiology of PsA are scarce. Studies from Europe estimate that the prevalence of PsA ranges from 0.16% to 0.32% (9). There is limited information about the population-based epidemiology of psoriasis and PsA in North America. An online survey conducted in Canada showed a prevalence of 1.0–3.1% of self-reported psoriasis in a sample from the general population. The estimated prevalence of PsA in these patients was 18% (10). The major limitation of this study was its reliance on self-reported diagnoses, which are associated with inaccuracies that can lead to misclassification of cases and controls.

Studying trends in the prevalence of psoriatic disease is important for understanding and projecting the burden of disease. Better knowledge of the epidemiology of psoriatic disease could improve health care planning and resource use. Therefore, the aim of this study was to estimate the population prevalence and incidence of psoriasis and PsA and their temporal trends, in Ontario, Canada.

PATIENTS AND METHODS

Data sources. In this population-based study, we used health administrative databases from Ontario, Canada representing 40% of the Canadian population, with 10.9 million adults in 2016 (11). All Ontarians are insured under a single-payer system, the Ontario Health Insurance Plan (OHIP), for hospital and physician services and procedures; however, outpatient prescription medications are funded only for social assistance recipients ages ≥65 years and for residents who have very high drug costs relative to their income. Health care encounters are recorded in

administrative health care databases, which are linked using an encoded health insurance number that is unique to each Ontarian eligible to receive insured health services in the province. These data were held securely and analyzed in linked, coded form at the Institute for Clinical Evaluative Sciences (ICES; www.ices.on.ca).

Using these data we conducted a retrospective populationbased cohort study from 2000 to 2015. We used the OHIP Claims History Database (12) to identify diagnosis codes for psoriasis and PsA on physician service claims. These diagnoses are coded using a modification of the International Classification of Diseases, Ninth Revision (ICD-9) (13). Information on physician specialty was obtained by linking the OHIP database to the ICES physician database. Hospital diagnoses for psoriasis and PsA were identified using the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed information regarding treatments and procedures rendered during all acute hospital admissions. Hospital data prior to 2002 have diagnoses coded in ICD-9 (13) and contain up to 16 diagnoses per hospital encounter. Hospitalizations after 2002 are coded using ICD-10 and contain up to 25 diagnoses per encounter. Here we included both primary and secondary hospital discharge diagnoses of psoriasis and PsA. Information regarding patients' demographic characteristics, vital status, and health insurance status were obtained from the OHIP Registered Persons Database. The linkage process is shown in Figure 1. Use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

Psoriasis and PsA case definition development and

validation. In order to develop algorithms for the identification of patients diagnosed with psoriasis and/or PsA, we derived a validation data set that was comprised of true-positive (psoriasis and/or PsA patients) and true-negative (patients without psoriasis or PsA) reference standards from primary care electronic medical records (EMRs). We identified 2,210 adult patients with suspected psoriasis and PsA through a targeted search for any possible psoriatic disease-related terms in the EMRs of a random sample of 30,424 patients in the primary care EMR Administrative Data Linked Database, which also is housed at ICES. The reference standard for classifying patients with physician-recorded psoriasis and/or PsA was confirmed using a retrospective chart abstraction. All 30,424 patients were then linked to health administrative data to assess the performance of the different algorithms combining physician billing and hospitalization diagnostic codes, medications, and procedures for identification of patients with psoriatic disease (14). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed for each algorithm. We decided a priori that the algorithm yielding the highest combination of PPV and sensitivity would be used to create psoriasis and PsA cohorts. The following algorithms were deemed optimal and used for the primary analysis: (for psoriasis) at least 1 diagnosis in hospitalization records OR at least 2 psoriasis diagnostic codes ever

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Algorithms to identify cases in administrative databases: Psoriasis:

1 diagnosis in hospitalization records

OR

• at least 2 psoriasis diagnostic codes ever assigned by any physician

PsA:

at least 1 diagnosis in hospitalization records

OR

 at least 1 psoriasis diagnosis code ever assigned by any physician AND at least 2 diagnosis codes of spondyloarthritis ever assigned with at least 1 assigned by a rheumatologist or internal medicine specialist

Canadian Institute for Health Information -Discharge Abstract Database (CIHI-DAD)

- Diagnosis of psoriasis or PsA during hospitalization

OHIP Registered Persons Database (RPDB)

- Vital status
- Demographics

Patient unique identification number

Ontario Health Insurance Plan (OHIP) Claims History Database

- Physician diagnosis of psoriasis or PsA

ICES Physician Database (IPDB)

- Physician specialty

Figure 1. Summary of case identification using the different administrative databases. PsA = psoriatic arthritis; ICES = Institute for Clinical Evaluative Sciences.

assigned by any physician (specificity 99%, sensitivity 52%, PPV 62%, NPV 100%); (for PsA) at least 1 diagnosis in hospitalization records OR a combination of at least 1 psoriasis diagnosis code ever assigned by any physician AND at least 2 diagnostic codes of spondyloarthritis ever assigned with at least 1 assigned by a rheumatologist or internal medicine specialist (specificity 100%, sensitivity 51%, PPV 65%, NPV 99%). We performed a sensitivity analysis to assess the changes in prevalence estimates of psoriasis and PsA when using a more stringent case definition that required 3 instead of 2 diagnostic codes for psoriasis and spondyloarthritis, respectively, and keeping the remaining terms the same.

Statistical analysis. The crude and age- and sexstandardized annual prevalence and incidence rates were calculated (with corresponding 95% confidence intervals [95% Cls]) for psoriasis and PsA by dividing the number of patients ages ≥20 years classified as having PsA by the number of Ontario residents ages ≥20 years. For psoriasis, this calculation was done annually for the period 2000–2015. For PsA, results are reported from 2008 onward due to the introduction of spondyloarthritis-specific billing codes in 2005, permitting a 3-year stabilization period for case accrual.

While the administrative data were available from 1990 onward, we introduced a 10-year run-in period to distinguish between incident and prevalent psoriasis patients, as prevalent cases would otherwise appear as incident when the data became available. Thus, the prevalence and incidence rates of psoriasis are reported from 2000 onward. For PsA a longer run-in period was used (due to changes in billing codes), and the results were reported from 2008 onward.

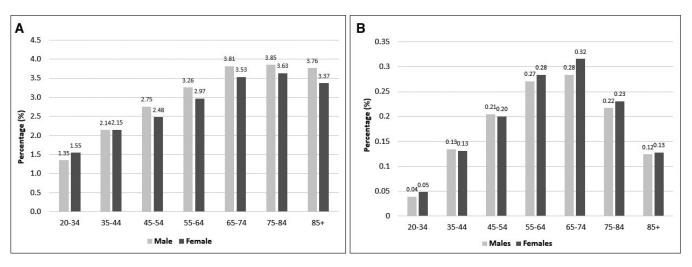


Figure 2. Age distribution of psoriasis (A) and psoriatic arthritis (PsA) (B) by sex in Ontario (2015).

In order to identify incident cases, disease onset was defined as the date of the first qualifying health services contact for which a diagnosis of psoriasis or PsA was provided. Prevalent cases remained in their respective cohorts from the date of their first qualifying diagnosis of psoriasis or PsA until they left the province, died, or reached the end of the study (December 2015). Annual sex- and age-specific prevalence and incidence rates were calculated for 10-year age groups and expressed as proportions using the 1991 Ontario population for direct age and sex standardization.

Due to the suboptimal PPV and sensitivity of the algorithms for psoriasis and PsA, we performed a sensitivity analysis that adjusted the prevalence and incidence rates of psoriasis and PsA based on the operating characteristics of each algorithm, to better estimate the number of true positive cases of psoriasis and PsA patients (14). Using data from our validation study, we estimated the number of true and false positive cases and controls (separately for psoriasis and PsA). We then estimated the false positive rate (FPR) and false negative rate (FNR) as follows:

Finally, the probability of having the disease in the general population was calculated by noting P(Algorithm+)=(1-FNR)P(Disease) + FPR(1-P(Disease)), giving a revised prevalence estimate of

$$P*(Disease) = \frac{P(Algorithm+) - FPR}{1 - FNR - FPR} =$$

When this revised estimate gave a negative value it was set to zero. The 95% CIs were calculated using nonparametric bootstrap resampling (15).

RESULTS

Prevalence and incidence of psoriasis. Among the 10,774,802 individuals ages ≥20 years living in Ontario in 2015, we identified 273,238 patients with a diagnosis of psoriasis according to our algorithm (7,541 incident cases), resulting in an overall crude prevalence of 2.54% (95% CI 2.53–2.55) and overall crude incidence of 69.9 (95% CI 68.4–71.6) per 100,000 population. The corrected prevalence of psoriasis remained similar at 2.76% but with a wider 95% CI (2.47–3.05). Psoriasis distribution was similar between males and females (male:female ratio 1.03). The age distribution of psoriasis patients is shown in Figure 2A.

Prevalence and incidence of PsA. Overall, 18,655 patients were identified with a diagnosis of PsA living in Ontario in 2015 (1,647 new diagnosis cases), which resulted in an overall crude prevalence of 0.173% (95% Cl 0.171–0.176) and incidence rate of 15.3 (95% Cl 14.6–16.0) per 100,000 population. The corrected prevalence of PsA remained similar at 0.206% (95% Cl 0.136–0.289). As with psoriasis, the prevalence of PsA was similar

Table 1. Crude and age- and sex-standardized prevalence and incidence of psoriasis in Ontario by year (2000–2015)*

		Prevale	nce per 100	Incidence per 100,000			
Year	Population	Psoriasis	Crude, %	Standardized, % (95% CI)†	New psoriasis	Crude	Standardized (95% CI)†
2000	8,768,082	156,430	1.78	1.74 (1.73–1.75)	9,873	112.6	111.1 (108.9–113.4)
2001	8,958,878	165,938	1.85	1.80 (1.79–1.81)	9,849	109.9	108.6 (106.5–110.8)
2002	9,094,208	174,689	1.92	1.86 (1.85-1.86)	9,203	101.2	99.7 (97.6-101.8)
2003	9,227,868	183,257	1.99	1.91 (1.90-1.92)	9,111	98.7	97.3 (95.3-99.3)
2004	9,355,095	191,840	2.05	1.97 (1.96-1.98)	9,060	96.8	95.3 (93.3-97.3)
2005	9,475,920	199,981	2.11	2.02 (2.01-2.03)	8,645	91.2	89.8 (87.9–91.8)
2006	9,593,910	208,362	2.17	2.07 (2.06-2.08)	8,979	93.6	92.7 (90.7-94.7)
2007	9,699,525	216,250	2.23	2.12 (2.11-2.12)	8,601	88.7	87.6 (85.7–89.6)
2008	9,829,603	223,919	2.28	2.15 (2.14-2.16)	8,585	87.3	85.9 (84.0-87.8)
2009	9,988,048	231,627	2.32	2.18 (2.17-2.19)	8,610	86.2	85.2 (83.4-87.1)
2010	10,124,330	238,879	2.36	2.21 (2.20-2.22)	8,399	82.9	81.8 (80.0-83.7)
2011	10,277,982	246,436	2.40	2.24 (2.23-2.25)	8,868	86.2	85.0 (83.2-86.9)
2012	10,425,784	254,041	2.44	2.26 (2.26-2.27)	8,883	85.2	83.9 (82.1-85.7)
2013	10,564,887	261,241	2.47	2.29 (2.28-2.30)	8,789	83.2	82.1 (80.3-83.9)
2014	10,655,455	267,594	2.51	2.31 (2.30-2.32)	8,212	77.1	76.1 (74.4–77.9)
2015	10,774,802	273,238	2.54	2.32 (2.31–2.33)	7,541	69.9	68.7 (67.1–70.3)

^{*} Values are the number, unless indicated otherwise. 95% CI = 95% confidence interval.

[†] Age- and sex-standardized to Ontario population in 1991.

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Table 2. Crude and age- and sex-standardized prevalence and incidence of psoriatic arthritis (PsA) in Ontario by year (2008–2015)*

		Prevalence	Incidence				
Year	Population	PsA	Crude, %	Standardized, % (95% CI)†	New PsA	Crude	Standardized (95% CI)†
2008	9,829,603	9,662	0.098	0.088 (0.086-0.090)	1,386	14.1	13.0 (12.3–13.7)
2009	9,988,048	10,833	0.108	0.097 (0.095-0.099)	1,278	12.8	11.8 (11.1–12.5)
2010	10,124,330	11,994	0.118	0.105 (0.103-0.107)	1,284	12.7	11.7 (11.1–12.4)
2011	10,277,982	13,176	0.128	0.113 (0.111-0.115)	1,338	13.0	11.8 (11.2–12.5)
2012	10,425,784	14,496	0.139	0.122 (0.120-0.124)	1,442	13.8	12.8 (12.1-13.5)
2013	10,564,887	15,881	0.150	0.131 (0.129-0.133)	1,542	14.6	13.2 (12.5-13.9)
2014	10,655,455	17,206	0.161	0.140 (0.138-0.142)	1,524	14.3	13.0 (12.3-13.7)
2015	10,774,802	18,655	0.173	0.149 (0.147-0.151)	1,647	15.3	14.0 (13.3-14.7)

^{*} Values are the number, unless indicated otherwise. 95% CI = 95% confidence interval.

in males and females (male:female ratio 0.94). The age distribution of patients with PsA is shown in Figure 2B.

Temporal trends of psoriasis and PsA. The crude and the age- and sex-standardized incidence rates from 2008 to 2015 are shown in Tables 1 and 2. The crude prevalence of psoriasis increased by approximately 45% during the study period, from 1.78% in 2000 to 2.54% in 2015 (Table 1). A similar increase was observed in the age- and sex-standardized psoriasis prevalence, from 1.74% in 2000 to 2.32% in 2015. The crude and age- and sex-standardized incidence rates showed a gradual decrease from 2000 to 2015 (standardized incidence rates per 100,000: 111.1 in 2000 and 68.7 in 2015). The prevalence rates increased to similar degrees in both sexes over time (data not shown). The temporal trends in sexstandardized prevalence and incidence of psoriasis by age groups are shown in Figure 3. A more pronounced increase in the prevalence of psoriasis was observed in the older age groups (ages ≥65 years).

A similar trend was observed in the prevalence of PsA, with doubling of the crude prevalence from 0.098% in 2008 to 0.173% in 2015. The changes in the age- and sex-standardized PsA prevalence were comparable (from 0.088% in 2008 to 0.149% in 2015). The crude and age- and sex-standardized incidence rates remained stable from 2008 to 2015 with approximately 13 to 15 per 100,000 population. The temporal trends in sex-standardized prevalence and incidence of PsA by age groups are shown in Figure 4. A more prominent increase in the prevalence of PsA was seen in the middle age and older individuals (ages >45 years).

Sensitivity analysis. A sensitivity analysis was performed to assess the changes in the prevalence of psoriasis and PsA when using more stringent algorithms, requiring 3 instead of 2 diagnostic codes for psoriasis and spondyloar-thritis for case definition. Using a more stringent definition, the estimated crude prevalence and incidence of patients with psoriasis and PsA living in Ontario in 2015 were psoria-

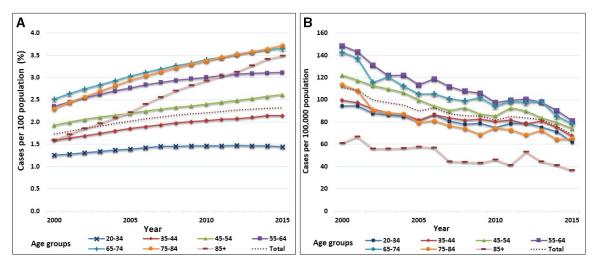
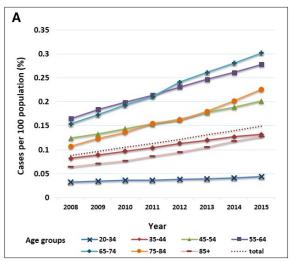


Figure 3. Sex-standardized temporal trends by age groups in the prevalence (A) and incidence (B) of psoriasis in Ontario from 2000 to 2015.

[†] Age- and sex-standardized to Ontario population in 1991.



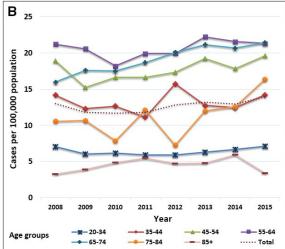


Figure 4. Sex-standardized temporal trends in the prevalence (A) and incidence (B) of psoriatic arthritis in Ontario from 2008 to 2015.

sis 1.71% (95% CI 1.71–1.72) and 36.1 (95% CI 34.9–37.2) per 100,000 population, respectively, and PsA 0.167% (95% CI 0.164–0.169) and 13.6 (95% CI 12.9–14.3) per 100,000 population, respectively.

A total of 18,655 patients with a diagnosis of PsA were identified living in Ontario in 2015 (1,647 new diagnosis cases), which resulted in an overall crude prevalence of 0.173% (95% CI 0.171–0.176) and an incidence rate of 15.3 (95% CI 14.6–16.0) per 100,000 population. The corrected prevalence of PsA remained similar at 0.206% (95% CI 0.136–0.289). As with psoriasis, the prevalence of PsA was similar in males and females (male:female ratio 0.94).

DISCUSSION

In this population-based study, we describe trends in the prevalence and incidence of psoriasis and PsA in Ontario over the past 15 years. In 2015, the prevalence of psoriasis and PsA in Ontario was 2.54% and 0.17%, respectively. The corresponding incidence rates were 69.9 and 15.3 per 100,000 population, respectively. The cumulative prevalence of both PsA and psoriasis has gradually increased over the past decade, while at the same time global incidence rates of both have either remained stable or slightly decreased.

The population-based epidemiology of psoriatic disease has been investigated mostly in European populations. Public health data about the epidemiology of psoriasis and PsA in North America are relatively limited and somewhat dated. The prevalence of psoriasis has been estimated to be between 0.5% and 3.15% of the US population (8). Information about the population prevalence of PsA in North America is scarce. In a phone survey that included 27,220 randomly selected individuals, the prevalence of PsA was found to be 0.25% (16). The primary limitation of population surveys is the use of a case definition of unknown

validity that relied on self-reported diagnosis of psoriasis and PsA. In a small population-based study (147 patients with PsA) that used an administrative database from Minnesota, in the US, the point prevalence of PsA was 0.16%, and the incidence was 7.2 cases per 100,000 population (17). Administrative health databases are increasingly used in Canada and abroad to evaluate the population burden of diseases. The public health care system in Canada, along with the availability of provincial databases, provides an opportunity to evaluate the prevalence and incidence of psoriatic disease at the population level.

To the best of our knowledge, this is the first large-scale population-based study of the prevalence of psoriasis and PsA in Canada. Our estimated prevalence of psoriasis in Ontario (2.54%) falls well within the prevalence range of physician-confirmed diagnosis of psoriasis reported from other population-based studies from Northern European countries of 1.3-2.84% and US studies showing a prevalence of 0.5-3.1% (8,18). Similarly, the prevalence of PsA (0.17%) was similar to previous reports of physicianconfirmed diagnosis of PsA from the US and Northern European countries (0.13-0.28%) (9). In accordance with previous reports, the prevalence of psoriasis and PsA in Ontario was higher than the prevalence in East Asian populations (<0.1% and <1.5%, respectively) (19,20). Overall, our estimated incidence rate of PsA of 15.3 cases per 100,000 population fell within previous estimates from other European populations, which ranged from 6.1 to 41.3 per 100,000 population (21-23). Similarly, the incidence rate of psoriasis (69.9 per 100,000 population) is close to previously reported incidence rates from European populations and higher than in East Asian populations (18). Variation in point estimates of prevalence and incidence may be partially attributed to methodologic differences among the published studies, but genetic and environmental factors also are important. In general, studies of self-reported diagnoses have shown higher prevalence estimates than those relying on medical records or health administrative data.

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Over time we estimated a steady increase in the prevalence of psoriasis and PsA in Ontario during the study period, while the incidence rate remained relatively stable (in PsA) or slightly decreased (in psoriasis). Studies from the UK, Norway, and Spain showed a similar temporal increase in the prevalence of psoriasis (24–27), and recent studies from Denmark and Israel (23,28) showed temporal increases in the prevalence and incidence of PsA. Springate et al (24) simultaneously examined trends in the incidence, prevalence, and mortality of patients with psoriasis in the UK over the past 15 years. They concluded that the observed temporal increase in prevalence was explained by the increasing survival of psoriasis patients, which results in a steady growth of the pool of patients. We are unable to prove or disprove such hypotheses with the current data.

Our case definitions for psoriasis and PsA are based on algorithms that underwent a rigorous process of validation. We selected algorithms that optimized PPV and sensitivity, as both are desirable properties when evaluating the prevalence of a disease in the general population. A few studies that evaluated the validity of psoriasis and PsA diagnostic codes in administrative databases have been published (29–33). The majority of the studies restricted their validation process to patients who were identified by a preselected algorithm, which may explain the higher PPV (ranging from 85% to 90%) compared to the algorithms used in our study (30–33). When using a methodology similar to ours for validation of psoriasis in EMR databases, Icen et al (29) found similar a PPV (68.7%), highlighting the inaccuracies of case definition and the need to consider these in studies showing the epidemiology of a disease using administrative data.

The primary strength of our study is the use of a centralized data resource in the setting of a public health system, with equal access to health care for the entire population. As with any study, there are important potential limitations to consider. First, the case definition is based on diagnostic coding from physicians and hospital records, and physicians possibly used these codes when trying to rule out the diagnosis. Second, we relied on documentation in the family physician EMR, and it is possible that family physicians did not accurately diagnose or record these conditions in their patient records. This potential may have led to misclassification of cases. To account for imperfect sensitivity and PPV, we provided corrected estimates of the prevalence that were based on the known properties of the algorithms (e.g., sensitivity and specificity). The corrected estimates were close to the initial uncorrected estimates. This agreement gives us confidence that our employed algorithm can be used to give reasonably accurate estimates of prevalence and incidence in large populations over time, but given the lack of sensitivity and PPV, the application of this algorithm probably can not be used to accurately identify individual patients with these disease conditions. Fourth, we could not capture patients with undiagnosed psoriasis and PsA. Last, we could only evaluate the trends in the occurrence of PsA since 2008 due to changes

in billing code practice in the years prior. The increase in the prevalence of PsA since 2008 may be partially explained by assigning new codes to prevalent PsA patients. In summary, we provide real-world data that enhance our understanding of the epidemiology of psoriatic disease in a population of more than 10 million adult individuals. The estimated prevalence of psoriasis and PsA appear to have gradually increased over time, highlighting the importance of the burden of psoriatic disease.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Eder had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Eder, Widdifield, Rosen, Cook, Alhusayen, Paterson, Cheng, Campbell, Bernatsky, Gladman, Tu.

Acquisition of data. Jabbari.

 $\mbox{\bf Analysis} \mbox{ and interpretation of data.} \mbox{ Eder, Widdifield, Cook, Lee, Paterson, Cheng, Jabbari, Tu.}$

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