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The Epidemiology of Rheumatoid Arthritis in Ontario, Canada

Jessica Widdifield,[1] J. Michael Paterson,[2] Sasha Bernatsky,[3] Karen Tu,[1] George Tomlinson,[4] Bindee Kuriya,[4] J. Carter Thorne,[5] and Claire Bombardier[4]

Objective. **Epidemiologic assessments of sufficiently large populations are required in order to obtain robust estimates of disease prevalence and incidence, particularly when exploring the influence of various factors (age, sex, calendar time). We undertook this study to describe the epidemiology of rheumatoid arthritis (RA) over the past 15 years.**

Methods. **We used the Ontario Rheumatoid Arthritis administrative Database (ORAD), a validated population-based research database of all Ontarians with RA. The ORAD records were linked with census data to calculate crude and age and sex–standardized prevalence and incidence rates from 1996 to 2010. Vital statistics were used to estimate annual all-cause mortality during the study period.**

Results. **As of 2010, there were 97,499 Ontarians with RA, corresponding to a cumulative prevalence of 0.9%. Age and sex–standardized RA prevalence increased steadily over time from 473 (95% confidence interval [95% CI] 469–478) per 100,000 population (0.49%) in 1996 to 784 (95% CI 779–789) per 100,000 population (0.9%) in 2010. Age and sex–standardized incidence per 100,000 population ranged from 62 (95% CI 60–63) in 1996 to 54 (95% CI 52–55) in 2010. All-cause mortality decreased by a relative 21.4% since 1996.**

Conclusion. **Over a 15-year period, we observed an increase in RA prevalence over time. This rise may be attributed to the increasing time to ascertain cases (which may have been latent in the population during earlier years of the study), increasing survival, and/or an increase in the aging background population. Incidence appears to be stable.**

Previous research has shown that rheumatoid arthritis (RA) affects ~0.5–1% of the general population. The prevalence and incidence may vary substantially according to various factors, including geographic location, patient sex and age, and calendar time (1). Some reports have indicated that RA prevalence may be decreasing (2–7), particularly among women (8,9). Other reports, however, have indicated that the prevalence has risen (and is projected to continue to increase) in Europe and North America as a function of an underlying aging population (10) and increasing survival (11). Conflicting data also exist with regard to secular trends in incidence, with some studies showing a rising incidence (12) and others showing a declining incidence (7,9,13,14). Some authors have reported a shift toward a more elderly age at onset (15,16), but such shifts have

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[1]Jessica Widdifield, BSc, PhD, Karen Tu, MD, MSc: University of Toronto and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; [2]J. Michael Paterson, MSc: University of Toronto and Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, and McMaster University, Hamilton, Ontario, Canada; [3]Sasha Bernatsky, MD, FRCPC, PhD: McGill University, Montreal, Quebec, Canada; [4]George Tomlinson, PhD, Bindee Kuriya, MD, FRCPC, MS, Claire Bombardier, MD, FRCPC: University of Toronto, Toronto, Ontario, Canada; [5]J. Carter Thorne, MD, FRCPC: Southlake Regional Health Centre, Newmarket, Ontario, Canada.

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Address correspondence to Jessica Widdifield, BSc, PhD, University of Toronto, 200 Elizabeth Street, 13EN224, Toronto, Ontario M5G2C4, Canada. E-mail: jessica.widdifield@utoronto.ca.

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not been observed by all (17). Further, given the relatively low prevalence of RA, study populations must be sufficiently large to obtain robust estimates, particularly when stratifying by age and sex.

Our primary goal in the present study was to estimate the prevalence, incidence, and all-cause mortality of RA in a universal public health care system over the past 15 years by using a validated population-based research cohort designed to include all individuals with RA living in Ontario, Canada's most populous province. We also aimed to quantify changes over time in RA prevalence, incidence, and all-cause mortality by age and sex.

PATIENTS AND METHODS

Setting and design. Canada's publicly funded health care system is universal and comprehensive for both hospital care and physicians' services. We performed a population-based cohort study in Ontario, Canada, which has a diverse, multicultural population.

Subjects and data sources. We used the Ontario Rheumatoid Arthritis administrative Database (ORAD), a validated population-based research database that aims to include all individuals with RA living in Ontario. Patients are included in the ORAD if they are admitted to a hospital with an RA diagnosis or have at least 3 Ontario Health Insurance Plan (OHIP) (18) physician service claims (over 2 years) with RA as the recorded diagnosis, with at least 1 of these claims originating from a musculoskeletal specialist (rheumatologist, orthopedic surgeon) or internist. The ORAD has high sensitivity (78%), specificity (100%), and positive predictive value (PPV) (78%) for identifying RA patients according to reviews of both primary care (19) and rheumatology medical records (20). The ORAD is developed from inpatient diagnosis codes identified using the Canadian Institute for Health Information Discharge Abstract Database, which contains detailed information regarding all hospital admissions (21). It also includes physician billing diagnosis codes identified in the OHIP Database (18). Physicians are reimbursed by submitting claims to the OHIP for medical services provided. One diagnosis code, representing the main "reason for the visit," is provided with each claim (11,18,22,23).

Records for individuals in the ORAD are also linked to the Ontario Registered Persons Database to obtain information regarding the patient's age, sex, place of residence, and vital status. Census and intercensus population estimates for 1991–2011 were obtained from Statistics Canada (24). These data sets are linked in an anonymous manner using encrypted health insurance numbers, and they have very little missing information (25).

Statistical analysis. We used the ORAD to calculate crude and age and sex–standardized prevalence and incidence rates (with corresponding 95% confidence intervals [95% CIs]) (26) among patients age ≥15 years over the period 1996–2010 (the years of data available in the ORAD). Disease onset is defined as the date of the first qualifying health services contact for which a diagnosis of RA is provided (20). Only individuals with no such previous contacts for RA were counted as incident cases for the relevant year, and the incident population at risk was calculated as the census population minus the prevalent cases from the previous year. The numerator represents all patients with RA, and the denominator represents all persons age ≥15 years living in Ontario for the relevant year. Prevalent cases were carried forward for each year, and persons who died or moved out of the province were excluded from the numerator and denominator. Individuals age <15 years were also excluded from both the numerator and the denominator.

Annual age-specific RA rates were computed for 10-year age bins and expressed per 100,000 population. Age-standardized rates reflect the number of RA patients who would have been diagnosed if the age-specific rates observed in the actual population had occurred in a standard population. The 1991 Ontario population was used as the standard population for direct age and sex standardization.

For our primary analysis, we used a 5-year "run-in" period to distinguish between incident and prevalent cases, allowing rates to be reported from 1996 onward. It is a standard of practice not to compute disease incidence and prevalence from 1991 to 1995, as administrative data are only available from 1991 onward and all patients with prevalent disease will appear as patients with incident disease during the early years of the study. Results are reported up until 2010 to allow for a 2-year "look forward" period to meet the terms of the case definition. Sensitivity analyses were performed to assess the impact on incidence and prevalence of varying the length of the run-in period and case ascertainment period (years of data), respectively.

We used vital statistics to estimate annual all-cause mortality in the ORAD during the study period (1996–2010) by dividing the number of deaths among individuals with RA each year by the number of individuals with RA in each year. To compare mortality rates over time, we standardized them for age and sex using the 2001 Ontario census population estimates. Age and sex–standardized all-cause mortality estimates are expressed as the number of deaths per 1,000 RA patients for each year of the study period. Age and sex–specific all-cause mortality rates were also determined. Age categories with small cell sizes were suppressed for patient confidentiality. We computed relative changes between 1996 and 2008 in the age and sex–standardized all-cause mortality rates in individuals with RA.

All analyses were performed at the Institute for Clinical Evaluative Sciences (www.ices.on.ca) using SAS software, version 9.2. The study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board in Toronto, Canada.

RESULTS

During the study period, the number of individuals age ≥15 years (the population denominator) increased from 8,720,499 in 1996 to 10,851,140 in 2010. The number of patients with RA increased from 42,734 to 97,499 over the same time period (Table 1). The crude prevalence doubled during the study period from 490 to 899 per 100,000 population. The crude number of

Table 1. Crude and age and sex–standardized prevalence and incidence of RA by year*

Year	Prevalence†					Incidence †				
	No. of RA cases	Population	Crude estimate	Crude %	Standardized rate (95% CI)‡	No. of new RA cases	Population	Crude estimate	Crude %	Standardized rate (95% CI)‡
1996	42,734	8,720,499	490	0.49	473 (469–478)	5,523	8,682,077	64	0.06	62 (60–63)
1997	46,961	8,828,425	532	0.53	509 (505–514)	5,546	8,785,669	63	0.06	61 (59–62)
1998	51,248	8,959,209	572	0.57	544 (540–549)	5,731	8,912,234	64	0.06	62 (60–63)
1999	55,398	9,085,331	610	0.61	576 (571–581)	5,662	9,034,053	63	0.06	60 (58–61)
2000	59,129	9,220,621	641	0.64	602 (597–607)	5,429	9,165,200	59	0.06	56 (55–58)
2001	62,795	9,390,567	669	0.67	625 (620–630)	5,495	9,331,423	59	0.06	56 (54–57)
2002	66,537	9,588,554	694	0.69	646 (641–651)	5,614	9,525,743	59	0.06	56 (54–57)
2003	69,997	9,779,736	716	0.72	662 (657–667)	5,414	9,713,187	56	0.06	52 (51–54)
2004	73,575	9,939,997	740	0.74	679 (674–684)	5,641	9,869,989	57	0.06	53 (52–55)
2005	77,330	10,100,741	766	0.77	697 (692–702)	5,815	10,027,150	58	0.06	54 (52–54)
2006	81,614	10,257,323	796	0.80	719 (714–724)	6,431	10,179,982	63	0.06	58 (57–60)
2007	85,706	10,410,695	823	0.82	738 (733–743)	6,220	10,329,070	60	0.06	55 (54–57)
2008	89,420	10,556,974	847	0.85	753 (747–758)	6,046	10,471,253	58	0.06	53 (52–54)
2009	93,558	10,708,605	874	0.87	769 (764–775)	6,490	10,619,171	61	0.06	56 (54–57)
2010	97,499	10,851,140	899	0.90	784 (779–789)	6,395	10,757,575	59	0.06	54 (52–55)

* RA = rheumatoid arthritis; 95% CI = 95% confidence interval.
† Crude and standardized rates are per 100,000 population.
‡ Standardized by age and sex based on 1991 census population.

incident cases identified each year was 5,523 patients in 1996 and 6,395 patients in 2010. The crude incidence rate per 100,000 population was relatively stable (64 in 1996, 59 in 2010) (0.06% per year overall), as shown in Table 1.

The age and sex–standardized RA prevalence per 100,000 population also showed a steady increase over time, from 473 (95% CI 469–478) in 1996 to 784 (95% CI 779–789) in 2010 (0.49% to 0.9%) (Table 1). There was a slight downward trend over time in age and sex–standardized incidence per 100,000, from 62 (95% CI 60–63) in 1996 to 54 (95% CI 52–55) in 2010, although incidence appeared to stabilize from 2000 onward.

Overall and sex-specific age-standardized prevalence and incidence of RA over the years 1996–2010 are illustrated in Figure 1. The prevalence increased in both sexes over time (in females, from 637 [95% CI 630–644] in 1996 to 1,062 [95% CI 1,054–1,070] in 2010; in males, from 291 [95% CI 286–298] in 1996 to 472 [95% CI 466–478] in 2010). A slight downward trend in incidence per 100,000 population was observed in both sexes over time (in females, from 81 [95% CI 78–83] in 1996 to 72 [95% CI 70–75] in 2010; in males, from 41 [95% CI 39–43] in 1996 to 34 [95% CI 32–35] in 2010).

Figure 2 illustrates the trends over time in sex-standardized prevalence and incidence of RA in 10-year age groups. We observed prevalence to increase more steeply with increasing age. Sex-standardized incidence

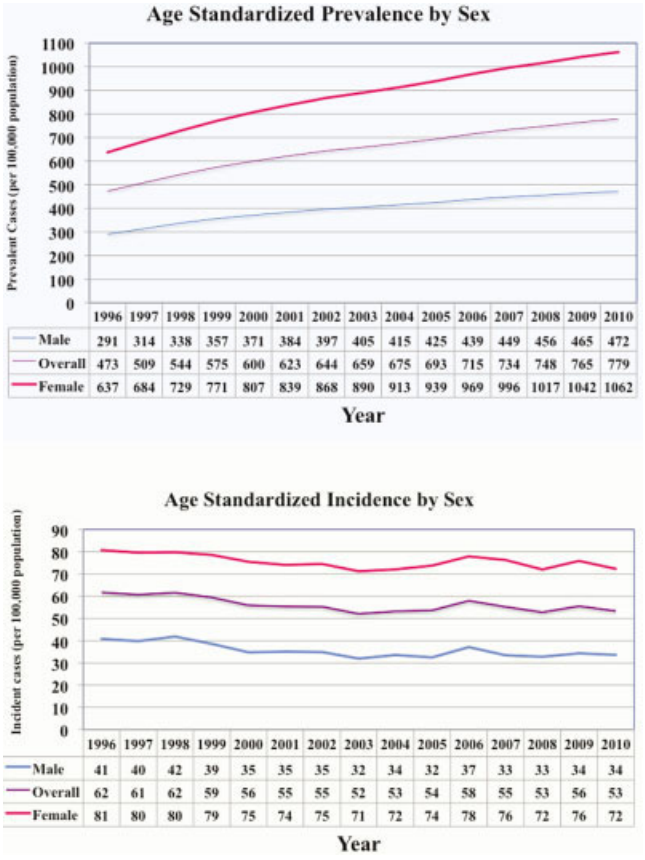

Figure 1. Age-standardized prevalence and incidence of rheumatoid arthritis by sex from 1996 to 2010.

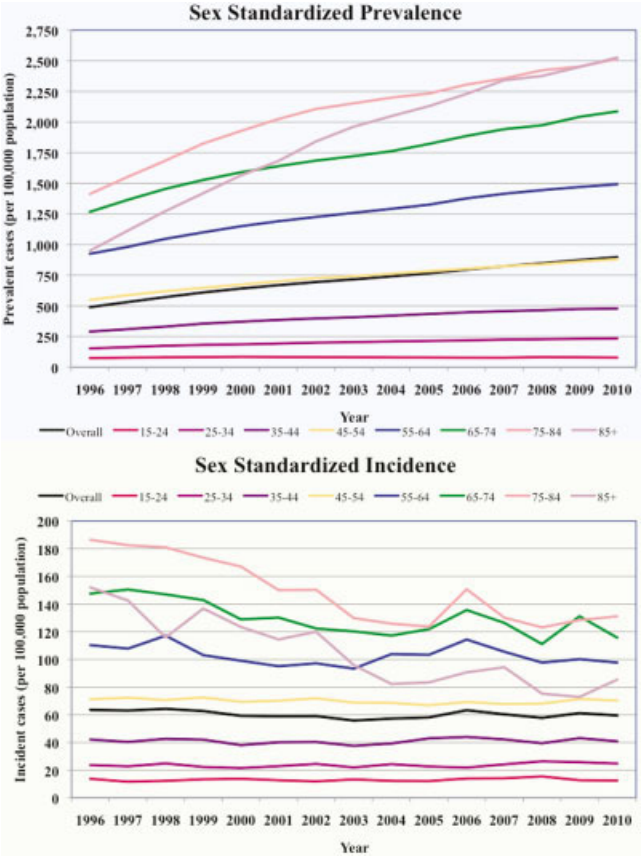

Figure 2. Sex-standardized prevalence and incidence of rheumatoid arthritis by age from 1996 to 2010.

was stable among adults age <65 years, but decreased among older persons over time.

In our sensitivity analyses using 10- and 15-year "run-in" periods, incidence in 2010 was estimated to be 58 and 55 (per 100,000), respectively, similar to our base-case rate of 54. With case ascertainment periods of 5 and 10 years, the prevalence estimates in 2010 were 555 and 664 (per 100,000), respectively, substantially lower than the 748 (per 100,000) with the 15-year case ascertainment period.

Age and sex–standardized all-cause mortality was 13.0 deaths per 1,000 RA patients in 1996 and 9.2 deaths per 1,000 RA patients in 2009 (Table 2). Age-specific all-cause mortality increased with increasing age, and was higher among males than females in all age groups. All-cause mortality decreased by a relative 21.4% from 1996 to 2008 (Table 3).

DISCUSSION

In the universal public health insurance system of Ontario, we studied trends from 1996 to 2010 in the prevalence, incidence, and all-cause mortality of RA—overall and by sex and age group. To our knowledge, the ORAD represents the largest validated population-based cohort of patients with RA in a universal health care system.

As of 2010, the prevalence of RA in Ontario was 0.9%. Our results are similar to RA prevalence estimates reported in British Columbia, Canada, and Minnesota (12,27). However, recent data from Swedish RA population registers showed a lower prevalence estimate of 0.77% (28), although the authors acknowledge that the prevalence may have been underestimated due to exclusion of RA patients not under the care of a rheumatologist. This underscores the importance of reporting and comparing case definitions to ascertain RA from population-based data, as varying methods can lead to different point estimates of disease.

Overall, we found that there are currently ~50 new cases of RA per year per 100,000 at risk. While this is mostly in keeping with population-based studies from other jurisdictions that on average report 25–50 new cases of RA per 100,000 (29), our data indicate that Ontario is at the upper end of this range. A recent study from the US showed that the overall age and sex–adjusted annual RA incidence was 40 cases per 100,000 population and that the incidence of RA increased moderately over time in women but not in men (12). One might expect those investigators to have captured slightly fewer individuals with RA than we did, as they required individuals to meet the 1987 revised classification criteria of the American College of Rheumatology (ACR) (30). The ACR criteria are not routinely used for diagnostic purposes, and patients are more likely to

Table 2. Age and sex–standardized all-cause mortality among individuals with RA by year*

Year	No. of deaths	RA population	Deaths per 1,000 (95% CI)
1996	1,458	46,961	13.0 (12.2–13.9)
1997	1,542	51,248	12.8 (11.8–13.8)
1998	1,721	55,398	12.7 (11.9–13.7)
1999	1,844	59,129	13.0 (11.9–14.2)
2000	1,888	62,795	12.3 (11.3–13.3)
2001	1,966	66,537	11.6 (10.9–12.3)
2002	2,074	69,997	11.8 (10.8–12.9)
2003	2,076	73,575	10.8 (10.1–11.6)
2004	2,158	77,330	10.5 (9.8–11.1)
2005	2,139	81,614	9.6 (9.0–10.1)
2006	2,347	85,706	10.5 (9.7–11.4)
2007	2,366	89,420	9.5 (8.8–10.3)
2008	2,461	93,558	10.2 (9.3–11.3)
2009	2,529	97,499	9.2 (8.4–10.0)

* See Table 1 for definitions.

Table 3. Age and sex–specific all-cause mortality among individuals with RA*

Group	1996			2000			2004			2008			Change from 1996 to 2008, %		
	No. of deaths	RA population	Death rate per 1,000 (95% CI)	No. of deaths	RA population	Death rate per 1,000 (95% CI)	No. of deaths	RA population	Death rate per 1,000 (95% CI)	No. of deaths	RA population	Death rate per 1,000 (95% CI)	Deaths	RA population	Death rate
Overall															
15–54	65	17,857	3.6 (2.8–4.6)	88	23,449	3.8 (3.0–4.6)	94	27,762	3.4 (2.7–4.1)	122	31,814	3.8 (3.2–4.6)	87.7	78.2	5.4
55–64	145	9,402	15.4 (13.0–18.1)	156	12,472	12.5 (10.6–14.6)	174	16,791	10.4 (8.9–12.0)	212	21,668	9.8 (8.5–11.2)	46.2	130.5	−36.6
65–74	396	11,203	35.3 (32.0–39.0)	446	13,664	32.6 (29.7–35.8)	435	15,668	27.8 (25.2–30.5)	463	18,838	24.6 (22.4–26.9)	16.9	68.2	−30.5
75–84	590	6,928	85.2 (78.4–92.3)	790	10,484	75.4 (70.2–80.8)	910	13,228	68.8 (64.4–73.4)	903	15,458	58.4 (54.7–62.4)	53.1	123.1	−31.4
85+	262	1,571	166.8 (147.2–188.2)	408	2,726	149.7 (135.5–164.9)	545	3,881	140.4 (128.9–152.7)	761	5,780	131.7 (122.5–141.4)	190.46	267.9	−21.1
All ages†	1,458	46,961	13.0 (12.2–13.9)	1,888	62,795	12.3 (11.3–13.3)	2,158	77,330	10.5 (9.8–11.1)	2,461	93,558	10.2 (9.3–11.3)	68.8	99.2	−21.4
Female															
15–54	35	12,859	2.7 (1.9–3.8)	54	16,811	3.2 (2.4–4.2)	62	20,047	3.1 (2.4–4.0)	81	23,211	3.1 (2.4–4.0)	131.4	80.5	13.6
55–64	87	6,511	13.4 (10.7–16.5)	107	8,673	12.3 (10.1–14.9)	103	11,813	8.7 (7.1–10.6)	133	15,280	8.7 (7.3–10.3)	52.87	134.68	−34.9
65–74	239	7,786	30.7 (26.9–34.8)	251	9,382	26.8 (23.5–30.3)	272	10,788	25.2 (22.3–28.4)	286	13,047	21.9 (19.5–24.6)	19.67	67.57	−28.6
75–84	404	5,109	79.1 (71.6–87.2)	553	7,722	71.6 (65.8–77.8)	606	9,558	63.4 (58.5–68.7)	576	10,910	52.8 (48.6–57.3)	42.57	113.54	−33.2
85+	209	1,273	164.2 (142.7–188.0)	315	2,181	144.4 (128.9–161.3)	402	3,040	132.2 (119.6–145.8)	544	4,427	122.9 (112.8–133.7)	160.29	247.76	−25.2
All ages‡	974	33,538	11.0 (10.2–11.9)	1,280	44,769	10.9 (9.9–12.0)	1,445	55,246	9.4 (8.7–10.1)	1,620	66,875	8.8 (8.0–9.6)	66.3	99.4	−20.4
Male															
15–54	30	4,998	6.0 (4.1–8.6)	34	6,638	5.1 (3.5–7.2)	32	7,715	4.2 (2.8–5.9)	41	8,603	4.8 (3.4–6.5)	36.7	72.1	−20.6
55–64	58	2,891	20.1 (15.2–25.9)	49	3,799	12.9 (9.5–17.1)	71	4,978	14.3 (11.1–18.0)	79	6,388	12.4 (9.8–15.4)	36.21	120.96	−38.4
65–74	157	3,417	46.0 (39.0–53.7)	195	4,282	45.5 (39.4–52.4)	163	4,880	33.4 (28.5–38.9)	177	5,791	30.6 (26.2–35.4)	12.74	69.48	−33.5
75–84	186	1,819	102.3 (88.1–118.1)	237	2,762	85.8 (75.2–97.5)	304	3,670	82.8 (73.8–92.7)	327	4,548	71.9 (64.3–80.1)	75.81	150.03	−29.7
85+	53	298	177.9 (133.2–232.6)	93	545	170.6 (137.7–209.1)	143	841	170.0 (143.3–200.3)	217	1,353	160.4 (139.8–183.2)	309.43	354.03	−9.8
All ages‡	484	13,423	15.5 (13.8–17.2)	608	18,026	14.2 (12.5–16.0)	713	22,084	12.0 (11.0–13.2)	841	26,683	12.1 (10.3–14.2)	73.76	98.79	−21.4

* See Table 1 for definitions.
† Age and sex–standardized to the 2001 Ontario population.
‡ Age-standardized to the 2001 Ontario population.

fulfill these criteria over time. Despite having more relaxed criteria, we did not observe an increasing incidence over time, even though one might expect incidence to increase over time with better diagnostics and recognition of RA. Furthermore, others have reported conflicting data illustrating a declining incidence over time (7,14), with several studies showing a shift toward a more elderly age at onset (15,16). Such a shift was not found in our study or in a study from Rochester, MN (17).

For RA incidence to increase with age and decrease with time among older individuals, given that the average age of the background population itself has increased, the declining incidence over time among older individuals in our study may be partly due to prevalent cases among these individuals being misclassified as incident cases during the early years of the study. In other words, our study may have overestimated incidence and underestimated prevalence in the earliest years of observation, and it may be that distinguishing incident and prevalent cases may be most problematic in the older age groups. Previous research has shown that estimating incidence from routinely collected health services data can be challenging, as patients who contribute more observation time have an increasing likelihood of being detected (31). While we tested variations in the years of data available and the corresponding influence on incidence, secular trends illustrating a statistically significant decrease over time may be an artifact of the data. Moreover, when we standardize by age and present yearly aggregated results, we are essentially taking the same weighted average every year of the age-specific rates. Thus, the increasing prevalence and decreasing incidence in the oldest age groups will cause the aggregate numbers to tend more toward increasing prevalence and decreasing incidence over calendar time (more than they would if the oldest age groups behaved like the younger age groups). However, in the absence of age standardization, the effect would be larger still, as an older population in the later years would put more weight on the older age groups in calculating the year-by-year incidence and prevalence. Finally, as standardized rates will also vary with the use of different standard populations, we have also reported age-specific rates, which enable more meaningful comparisons across studies.

We observed a 21% relative decrease in all-cause mortality among RA patients between 1996 and 2008. A recent systematic review and meta-analysis showed that mortality has decreased among RA patients over the past decades (11). Our observed decline in mortality over time has several plausible mechanisms. First, we studied mortality during the modern era when early and aggressive treatment with disease-modifying antirheumatic drugs and subsequent biologic therapies are routinely the standard of practice. Several studies have shown a significant decline in the risk of death following treatment (32,33), which suggests that reducing the inflammatory burden and disease severity may be responsible for prolonging survival. Second, it has been suggested that the natural history of RA itself may be changing and becoming a milder, more indolent process (34). Third, declining mortality rates over time may be in part due to advances in the recognition of RA symptoms, earlier time-to-diagnosis and timely treatment, and better overall access to health care. Furthermore, heightened awareness of the risk of comorbidity in RA over recent years may have led to improved surveillance and treatment of conditions, such as cardiovascular disease, that previously conferred a substantially increased risk of death in RA (35).

Our study has both strengths and potential limitations. We used rigorous approaches to the validation and creation of the ORAD (19,20) by applying an administrative data algorithm that has the highest possible PPV while maximizing sensitivity and specificity. In addition, this is the largest epidemiologic study of RA in a universal health care system performed to date. We also used methods consistent with those of other studies examining trends in incidence and prevalence of chronic disease using validated population-based databases in Ontario (36–38). Our prevalence findings are consistent with those from a previously performed chart audit among a random sample of 7,500 patients seen in primary care (19). We attempted to accurately define incident cases; however, some of our incident cases may in fact have been prevalent cases (especially during the early years of the study). To address this potential bias, we applied a 5-year run-in period to reduce the possible misclassification of prevalent cases as incident ones. Testing variations of the run-in period suggests that part of the increase in prevalence over time may be attributed to the increasing time to ascertain cases (which may be latent in the population during earlier years of the study). Furthermore, as part of our previous validation exercises, we found that disease onset is fairly well defined in health services data (20).

The main limitation of our study is that health services data can only assess RA patients who sought and had access to health care providers. Therefore, we were unable to assess the population of patients who rarely access care, and it is important to view our data as

physician-identified prevalence, particularly specialist-identified RA. In addition, as our algorithm does not have 100% sensitivity in capturing RA, the ORAD may miss some RA patients, such as those who had active disease prior to the collection of administrative data, or those whose symptoms have resolved and who for these or other reasons are no longer seeking care for their RA. Similarly, when using health services data, fee-for-service remuneration can drive coding practice when incentives exist for the recording of specific diagnostic codes. While there have been modifications to billing policies affecting rheumatology-specific billing practices in Ontario over the past decade, we did not observe significant increases in prevalence during any of these time points. Furthermore, the ORAD currently does not contain information on important risk factors for RA, such as ethnicity or autoantibody status, and we were unable to explore the effects of specific factors on the epidemiology of RA.

In conclusion, RA prevalence increases with age and is highest among females. As of 2010, RA prevalence rates have also increased significantly since 1996. Factors contributing to the increase in prevalence over time may be attributed to the increasing time to ascertain cases, increasing survival, and an increase in the aging background population. Incidence appears to be slowly declining over time or stabilizing over the past decade, with a shift toward fewer patients with elderly age at onset.

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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 published. Dr. Widdifield 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. Widdifield, Paterson, Bernatsky, Bombardier.

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