# Incidence of cirrhosis in young birth cohorts in Canada from 1997 to 2016: a retrospective population-based study

*Jennifer A Flemming, Yvonne Dewit, Jeffrey M Mah, James Saperia, Patti A Groome, Christopher M Booth*

## Summary

**Background** Recent data show that the prevalence of chronic liver disease and cirrhosis is increasing in adolescents and young adults in the USA. We aimed to describe the epidemiology of cirrhosis using an age-period-cohort approach to define birth-cohort effects on the incidence of cirrhosis in Ontario, Canada.

**Methods** We did a retrospective population-based cohort study in Ontario, Canada, using linked administrative health data from the databases of ICES, formerly the Institute for Clinical Evaluative Sciences. Patients aged at least 18 years with cirrhosis were identified by use of a validated case definition (defined as at least one inpatient or outpatient visit with a diagnosis of cirrhosis or oesophageal varices without bleeding). We calculated annual standardised incidence and prevalence in the general population. We used an age-period-cohort approach to assess the independent association between birth cohort and incidence of cirrhosis in men and women.

**Findings** Between Jan 1, 1997, and Dec 31, 2016, 165 979 individuals with cirrhosis were identified. The age-standardised incidence increased over the study (from 70·6 per 100 000 person-years in 1997 to 89·6 per 100 000 person-years in 2016) as did the prevalence (from 0·42% in 1997 to 0·84% in 2016). Using age-period-cohort modelling and the median birth year as the reference, the incidence of cirrhosis was higher in participants born in 1980 (incidence rate ratio 1·55, 95% CI 1·50–1·59, p<0·0001); and in participants born in 1990 (2·16, 95% CI 2·06–2·27, p<0·0001) compared with a person of the same age born in 1951. The increase in incidence of cirrhosis was greater in women than in men (eg, women born in 1990: 2·60, 95% CI 2·41–2·79; men born in 1990: 1·98, 1·85–2·12).

**Interpretation** The incidence of cirrhosis has increased over the past two decades, and more so in younger birth cohorts and in women. Future studies to define the cause and natural history of cirrhosis in these groups are essential to develop strategies that could reverse these trends for future generations.

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**Departments of Medicine** (J A Flemming MD, J M Mah BHSc, J Saperia MD), **Public Health Sciences** (J A Flemming, Prof P A Groome PhD, Prof C M Booth MD), **and Oncology** (Prof C M Booth); **Queen's University, Kingston, ON, Canada; and ICES, Queen's University, Kingston, ON, Canada** (J A Flemming, Y Dewit MSc, Prof P A Groome, Prof C M Booth)

Correspondence to: Dr Jennifer A Flemming, Departments of Medicine and Public Health Sciences, Queen's University, Kingston Health Sciences Centre,Kingston, ON K7L 5G2, Canada **jennifer.flemming2@kingstonhsc.ca**

## Introduction

Cirrhosis is the final common pathway for all chronic liver diseases. It is the 12th leading cause of mortality worldwide, accounting for more than 1 million deaths in 2010, and is a major reason for years of life lost.[1] The burden of disease varies globally, with the highest mortality observed in central Asia, central and eastern Europe, and central Latin America, driven mostly by alcohol consumption and viral hepatitis.[2] Additionally, cirrhosis is associated with lower health-related quality of life and employment and represents a substantial economic burden, with an estimated direct cost of US$2·5 billion in the USA in 2004.[3,4] However, it is often underappreciated that cirrhosis disproportionally affects young adults.[5] In 2014, cirrhosis was the fifth leading cause of death in Americans aged 45–54 years and the sixth leading cause in those aged 35–44 years (behind only injuries, suicide, heart disease, and cancer),[6] with mortality due to cirrhosis increasing most in those aged 25–34 years from 1999 to 2016.[7] Data from the National Health and Nutrition Examination Survey (NHANES) show an increase in the prevalence of chronic liver diseases in adolescents and young adults over the past several decades.[8] In the NHANES study, chronic liver disease in Americans aged 15–39 years more than doubled from 12·9% in 1988–94 to 28·5% in 1999–2004, mainly because of non-alcoholic fatty liver disease (NAFLD). Additionally, a recent population-based study from Olmstead County (MN, USA) showed that the incidence of NAFLD increased most in those aged 18–39 years in 1997–2014.[9] Finally, liver transplantation for NAFLD in the USA increased by 14% annually in 2002–12 in patients who were younger than 40 years at the time of transplantation.[10]

Despite increasing evidence that the burden of chronic liver disease is growing in young adults, to our knowledge, no epidemiological studies have described the incidence of cirrhosis in the 21st century in the general population. Previous data from the UK suggest that the incidence of cirrhosis increased by 45% from 1992 to 2001.[11] The most comprehensive study from North America looking at the epidemiology of cirrhosis has come from the Veterans

## Research in context

### Evidence before this study

Using PubMed and EMBASE, we searched for literature on the epidemiology of cirrhosis around the world using keywords of "cirrhosis" AND "epidemiology" AND "incidence" AND "prevalence" AND "general population". Studies from Jan 1, 1990, to Dec 31, 2016, that included adults with cirrhosis from any country and in any language were assessed. Although studies have shown that the prevalence chronic liver disease and mortality secondary to cirrhosis is increasing in young adults, we found only two studies that described the incidence of cirrhosis. The first was a population-based study from the UK from 1992 to 2001 showing that the incidence of cirrhosis had increased by 45%. The second was from the Veterans Affairs population in the USA and suggested that the incidence of cirrhosis was stable from 2001 to 2013.

### Added value of this study

Our study adds to the literature in several ways. Previous work from the UK is now outdated as the study period ended in 2001. The work from the USA was from the Veterans Affairs population, 95% of whom are men. Our study cohort describes the incidence of cirrhosis in the general population in a contemporary era and therefore has strong external validity. Importantly, we were able to describe trends in the incidence of cirrhosis in both women and young adults. The results of this study suggest that both the incidence of cirrhosis has increased from 1997–2016. The increase in cirrhosis incidence was most significant in birth cohorts born after the baby-boomer generation and in women.

### Implications of all the available evidence

Over the past 20 years the incidence of cirrhosis has been increasing and the increase is highest in young birth cohorts and in women. The face of cirrhosis appears to be changing, and strategies to increase awareness of this silent epidemic in young adults and women are needed. Future studies able to define the cause and natural history of cirrhosis in these groups are essential to develop strategies that could reverse these trends for future generations.

Affairs (VA) population.[12] These data revealed that, although the incidence of cirrhosis overall has remained stable over the past decade, cirrhosis secondary to chronic hepatitis C and NAFLD has increased. However, given the VA population is more than 95% older men; the current epidemiology of cirrhosis in women and young adults remains unclear.

See Online for appendix

One way to describe the epidemiology of cirrhosis in young adults is to examine birth-cohort effects. A birth cohort refers to a group of individuals born during a given period within a specified geographical region. Birth-cohort effects refer to the experience or exposure of these groups over time and can be used to describe the incidence of disease that arises from exposures that affect age groups differently. Therefore, analysis of birth cohorts is an ideal way to describe the epidemiology of cirrhosis in young adults. Age-period-cohort modelling is a quantitative method used to enhance the understanding of disease trends by attempting to disentangle factors that influence all ages, such as changes in medical practice (period effects), from those that vary by generation (cohort effects), in addition to the influence of age (age effects).[13,14] Studies using age-period-cohort analysis have uncovered important birth-cohort effects related to the epidemiology of gastric cancer[15] and colorectal cancer in young Americans.[16]

The aim of our study is to describe the epidemiology of cirrhosis in Ontario, Canada, from 1997 to 2016, and use an age-period-cohort approach to explore the extent to which birth-cohort effects influence the incidence of cirrhosis.

## Methods

### Study design and participants

We did a retrospective population-based study of routinely collected health data from Ontario, Canada, from the databases of ICES, formerly the Institute for Clinical Evaluative Sciences. Ontario constitutes more than a third of the Canadian population, with approximately 13·5 million individuals, is ethnically diverse, and has a single-payer universal health insurance programme called the Ontario Health Insurance Plan (OHIP). All individuals in Ontario eligible for OHIP are assigned a unique ICES identification number that allows for direct linkage at the individual level to all other ICES databases (appendix p 5). This study used OHIP billing data compiled by the Ontario Ministry of Health and Long-Term Care to identify outpatient clinic visits, the Discharge Abstract Database (DAD) from the Canadian Institute for Health Information to identify hospital admissions, the National Ambulatory Care Reporting System (NACRS) to identify emergency room, day surgery, and hospital-based ambulatory care visits, and the Registered Persons Database (RPDB), which contains basic demographic information about any person who has ever registered for OHIP. OHIP data were also used to identify patients with diabetes using a previously validated definition (≥2 OHIP billings with an International Classification of Disease diagnostic code of 250 within a 2-year period).[17] To measure comorbidity, we used hospital admission data to calculate the Charlson-Deyo index[18] with a 2-year lookback window from when the patient was first identified to have cirrhosis. We described patient age and sex using data from the RPDB. Neighbourhood income quintile was identified using Canadian census data and was used as a marker of socioeconomic status. We also used census data to identify population numbers to calculate incidence and prevalence. All datasets were linked at the individual level with analyses conducted at the ICES satellite at Queen's University, ON, Canada. This study was approved by the

| | Overall (n=165 979) | Greatest generation (before 1925; n=8877) | Silent generation (1925–44; n=49 226) | Baby-boomers (1945–65; n=80 268) | Generation X (1966–79; n=20 507) | Millennials (1980 or later; n=7107) |
|---|---|---|---|---|---|---|
| Age* | 57 (47–68) | 82 (78–87) | 70 (65–70) | 53 (58–59) | 38 (33–43) | 25 (21–29) |
| Diabetes | 59 724 (36%) | 3521 (40%) | 23 728 (48%) | 27 708 (35%) | 4071 (20%) | 696 (10%) |
| Sex | | | | | | |
| Women | 67 056 (40%) | 4375 (49%) | 20 026 (41%) | 30 582 (38%) | 8639 (42%) | 3397 (48%) |
| Men | 98 923 (60%) | 4496 (51%) | 29 200 (59%) | 49 686 (62%) | 11 868 (58%) | 3710 (52%) |
| Charleston-Deyo comorbidity index | | | | | | |
| 0 | 136 424 (82%) | 5785 (65%) | 36 396 (74%) | 68 744 (86%) | 18 820 (92%) | 6679 (94%) |
| 1–3 | 22 469 (14%) | 2366 (27%) | 9320 (19%) | 9021 (11%) | 1386 (7%) | 376 (5%) |
| ≥4 | 7086 (4%) | 720 (8%) | 3510 (7%) | 2503 (3%) | 301 (2%) | 52 (1%) |
| Income quintile† | | | | | | |
| 1 (lowest) | 39 780 (24%) | 2139 (24%) | 11 352 (23%) | 19 462 (24%) | 5044 (25%) | 1783 (25%) |
| 2 | 35 345 (21%) | 1984 (22%) | 10 682 (22%) | 16 925 (21%) | 4271 (21%) | 1483 (21%) |
| 3 | 32 278 (19%) | 1693 (19%) | 9660 (20%) | 15 382 (19%) | 4179 (20%) | 1364 (19%) |
| 4 | 30 113 (18%) | 1471 (17%) | 8854 (18%) | 14 602 (18%) | 3875 (19%) | 1311 (18%) |
| 5 (highest) | 27 496 (17%) | 1550 (18%) | 8446 (17%) | 13 384 (17%) | 3009 (15%) | 1107 (16%) |
| Missing | 967 (1%) | 34 (1%) | 232 (1%) | 513 (1%) | 129 (1%) | 59 (1%) |
| Cause of cirrhosis | | | | | | |
| Viral hepatitis | 67 387 (41%) | 1875 (21%) | 15 298 (31%) | 38 849 (48%) | 9010 (44%) | 2391 (34%) |
| NAFLD or cryptogenic | 66 391 (40%) | 5264 (59%) | 21 751 (44%) | 26 226 (33%) | 9127 (45%) | 4056 (57%) |
| Alcohol | 28 050 (17%) | 1316 (15%) | 10 463 (21%) | 13 596 (17%) | 2078 (10%) | 534 (7%) |
| Autoimmune or genetic | 4151 (2%) | 416 (5%) | 1714 (4%) | 1597 (2%) | 292 (1%) | 126 (2%) |

Data are n (%) or median (IQR). NAFLD=non-alcoholic fatty liver disease. *Age in years at cirrhosis diagnosis. †Neighbourhood income quintiles.

***Table 1:*** **Demographics of patients with cirrhosis at index diagnosis in Ontario, Canada, in 1997–2016**

Queen's University Health Sciences Research Ethics Board (DMED-1651-13).

## Outcomes

The case definition used to identify cirrhosis in ICES data was based on a validation study.[19] In brief, individuals were defined as having incident cirrhosis if they had at least one inpatient or outpatient visit with a diagnosis of cirrhosis or oesophageal varices without bleeding (International Classification of Disease [ICD]-10-CA codes: K746, K745, K703, I859, I982; ICD-9 codes: 571.2, 571.5, 456.1; or OHIP code: 571) with an associated sensitivity of 97% and specificity of 77%. On the basis of earliest complete administrative data, a cohort of prevalent cases of cirrhosis was identified using inpatient visits as early as April 1, 1988, and outpatient visits starting on July 1, 1991, ending on December 31, 2016. This cohort included all Ontario residents eligible for OHIP who were aged at least 18 years at the first visit for cirrhosis on record. Patients with a first visit between Jan 1, 1997, and Dec 31, 2016, were defined as incident cases. This start date was chosen to distinguish between incident and prevalent cases by allowing a minimum lookback window of 5 years for both inpatient and outpatient visits. This time frame was chosen because our clinical experience suggests that patients with cirrhosis are likely to contact the health-care system at least once every 5 years.

Potential causes of cirrhosis were identified for all incident cases using both ICD and OHIP billing codes from the DAD, OHIP, and NACRS datasets (appendix p 1). The algorithm used was modified from previous work describing cirrhosis aetiology using administrative data.[12] First, codes for viral hepatitis were assessed. Since OHIP billing codes are unable to differentiate between hepatitis C and hepatitis B, these conditions were reported together as viral hepatitis. However, we assumed that most viral hepatitis reports represented hepatitis C because the prevalence of hepatitis C in Canada has been reported to be over five times higher than that of hepatitis B.[20] If no code for viral hepatitis was recorded, codes for autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency were considered. If identified, they were grouped together in the autoimmune or genetic category. Next, codes for alcohol-related liver disease and alcohol misuse were considered and, if found, were classified as alcohol related. If none of the above were identified, the remainder were classified as NAFLD or cryptogenic, given that the diagnosis of NAFLD in clinical practice is of exclusion of other chronic liver diseases, and the natural history and risk factors for NAFLD and cryptogenic cirrhosis have been found to be similar.[21]

A birth cohort is a group of individuals born in the same time frame and raised in the same environment. Using the year of birth for each individual obtained from the RPDB, the following birth-cohort definitions were used in our study: "greatest generation", born before 1925; "silent generation", born 1925–44; "baby-boomer

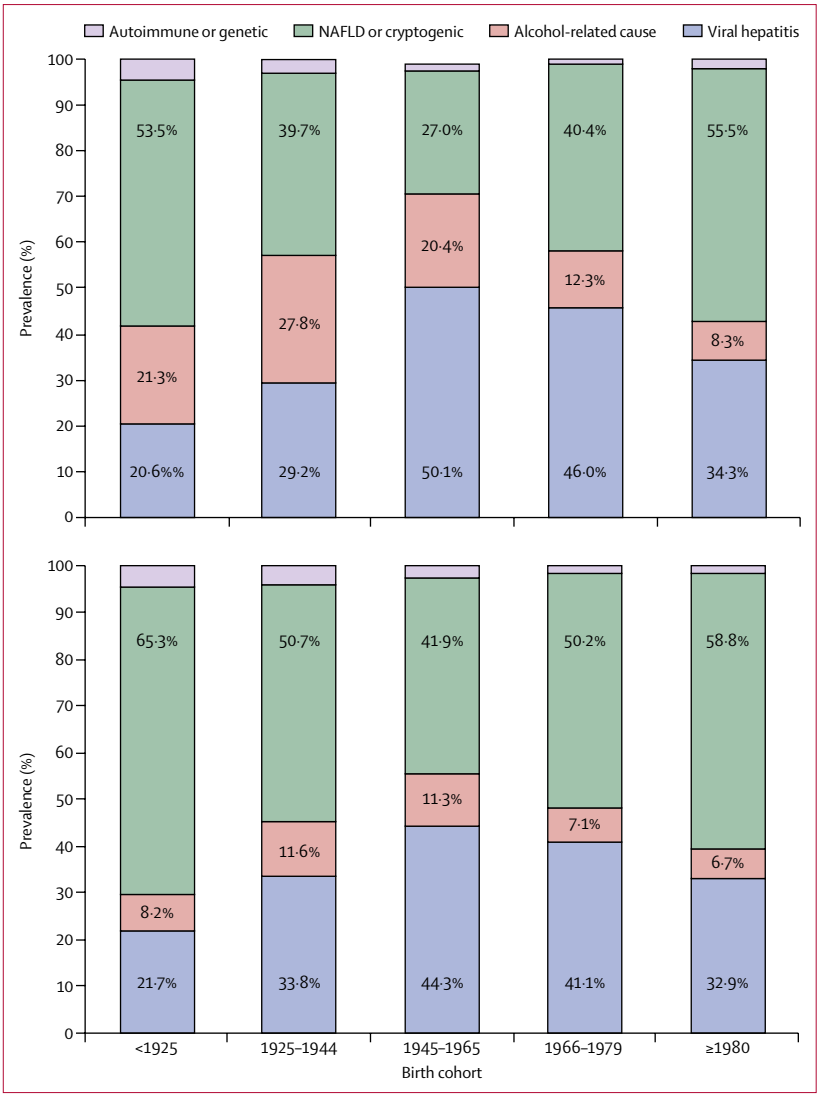


***Figure 1:*** **Causes of cirrhosis based on sex and birth cohort in Ontario, Canada, in 1997–2016**
(A) Men (n=98 923). (B) Women (n=67 056). NAFLD=Non-alcoholic fatty liver disease.

generation", born 1945–65; "generation X", born 1966–79; and "millennials", born in 1980 or later.

### Statistical analyses

Demographic and clinical characteristics of the cohort were described using cross-tabulations and measures of central tendency. Variables with missing data were reported as a percentage of the total cohort. Differences in causes of cirrhosis on the basis of birth cohort and sex were assessed using $\chi^2$ analysis. Annual sex-specific, age-specific, and cohort-specific incidence and prevalence rates were calculated from 1997 to 2016 by identifying the number of cases per group, and dividing by the corresponding census-based population figures. We calculated standardised incidence and prevalence from 1997 to 2016 using methods similar to those in other chronic diseases using administrative data from Ontario with a 95% CI calculated with the Wilson method.[22,23]

Age-period-cohort effects for the incidence of cirrhosis were modelled for 1997–2016. The association between age, period, and cohort is exact (ie, age=period–cohort). Because of this dependency, we could not identify a solution by simultaneous modelling of these three parameters using standard regression analyses, which would have resulted in over-parameterisation and subsequent exclusion of one of the variables.[13,24] To overcome this identifiability problem, we estimated a so-called drift variable for the overall log-linear trend in incidence of cirrhosis to reflect the sum of period and cohort effects.[14,24] Cohort and period effects were estimated using attributable deviations from log-linear trends, which were not dependent on any model constraint.[23] To detect non-linear effects, incidence and incidence rate ratios (IRRs) were estimated using parametric smooth functions based on cubic splines[14] with five knots each for age, birth cohort, and period. All modelling was done in Stata (version 12.1) using the *APCfit* command.[13] The age effects are described as the age-specific of cirrhosis per 100 000 person-years. The period rate ratios are 1 on average with a slope of 0 and are relative to the age-cohort prediction. The birth-cohort effects are described as cirrhosis IRRs using the median birth year of the entire cohort (1951) as the reference, with adjustment for the effect of age and period of diagnosis—ie, the birth-cohort IRRs are interpreted as the independent risk of cirrhosis based on the year of birth in a person of the same age relative to being born in 1951. To account for the effect of sex, we fitted two separate models, one for men and one for women, which is theoretically equivalent to fitting a full interaction for sex with all the spline terms.[14]

Finally, we did a sensitivity analysis of cirrhosis incidence using the age-period cohort model by use of a cirrhosis case definition with a higher specificity than that in the main analyses (two outpatient or one inpatient diagnosis of cirrhosis or non-bleeding varices; case definition 85% sensitivity and 94% specificity).

### Role of the funding source

The study sponsors had no role in the study concept, design, interpretation of the data, manuscript writing or decision to submit for publication. JAF and YD had full access to the raw data. The corresponding author had the final responsibility for the decision to submit for publication.

## Results

Between Jan 1, 1997, and Dec 31, 2016, we identified 165 979 individuals with incident cirrhosis (table 1). The median age at diagnosis was 57 years (IQR 47–68) and 98 923 (60%) patients were men. The relative proportion of men with cirrhosis was highest in the baby-boomer generation (49 686 [62%] men *vs* 30 582 [38%] women) and almost equal in the millennial generation (3710 [52%] men *vs* 3397 [48%] women). The greatest burden of cirrhosis

was in the baby-boomer birth cohort (80 268 [48%]). 20 507 individuals from the generation X cohort and 7107 individuals from the millennial birth cohort were diagnosed with cirrhosis before the age of 50 years. The most common cause of cirrhosis was viral hepatitis (67 387 [41%]), followed by NAFLD or cryptogenic cause (66 391 [40%]) and alcohol-related disease (28 050 [17%]). The cause of cirrhosis varied based on both birth cohort ($p<0·0001$) and sex ($p<0·0001$; figure 1). As expected, the baby-boomer cohort had the highest burden of viral hepatitis (38 849 [48%]). Overall, alcohol-related causes were more common in men than in women (figure 1). However, these differences were most pronounced in birth cohorts born before 1965, with men and women in the millennial birth cohort having similar proportions of alcohol-related cirrhosis (590 [8·3%] *vs* 476 [6·7%]). NAFLD or cryptogenic aetiology was most common in the greatest generation (5264 [59·3%]) and millennial cohort (4056 [57·1%]; table 1).

The overall incidence of cirrhosis increased by 22% (age-specific incidence 70·6 per 100 000 person-years in 1997 *vs* 89·6 per 100 000 person-years in 2016; figure 2), whereas the overall prevalence doubled (age-standardised prevalence 0·42% in 1997 *vs* 0·84% in 2016; figure 2). When assessed according to birth cohort, the prevalence in 2016 was highest in the greatest generation at 2·18% (95% CI 2·04–2·32), followed by the silent generation at 1·91% (1·89–1·94). Almost one out of every 500 millennials was living with cirrhosis (age-standardised prevalence 0·19%, 95% CI 0·18–0·19). Adjusted incidence (p 2) and prevalence (pp 3–4) of cirrhosis for selected years overall and by sex are shown in the appendix. The incidence of cirrhosis at any given age was higher in the baby-boomer generation than for those from the silent generation (figure 3). For example, the incidence of cirrhosis at age 60 years was 161·7 per 100 000 person-years for someone born from 1945–65 compared with 127·7 per 100 000 person-years for those born 1925–44 (table 2). At age 35 years, for which the three birth cohorts had overlapping data, the incidence of cirrhosis was higher in generation X (40·5 per 100 000 person-years) and Millennials (46·9 per 100 000 person-years) than in the baby-boomer generation (32·6 per 100 000 person-years; table 2, figure 3).

The age-period-cohort modelling showed a higher risk of cirrhosis with increasing age, with a peak incidence at approximately age 75 years for both men and women (figure 4). The period effects had a U-shaped distribution, suggesting an increase in cirrhosis diagnosis both at the beginning and the end of the study period. After adjusting for the effects of age and the period of cirrhosis diagnosis, a same-aged silent generation individual born in 1925 had a 27% lower risk of cirrhosis and an individual from the baby-boomer cohort born in 1945 had a 12% lower risk of cirrhosis than an individual born in 1951 (figure 4, table 3). However, compared with the 1951 reference birth year, the risk of cirrhosis was 31% greater in a same-aged generation X member born in 1966, 55% greater in millennials born in 1980, and 116% greater in millennials born in 1990. After adjusting for period of cirrhosis diagnosis and age, the incidence of cirrhosis increased over the study for both sexes; however, the trend was steeper in women, who had a risk of cirrhosis 2·5 times greater if they were born in 1990 than for those born in 1951 (figure 4).

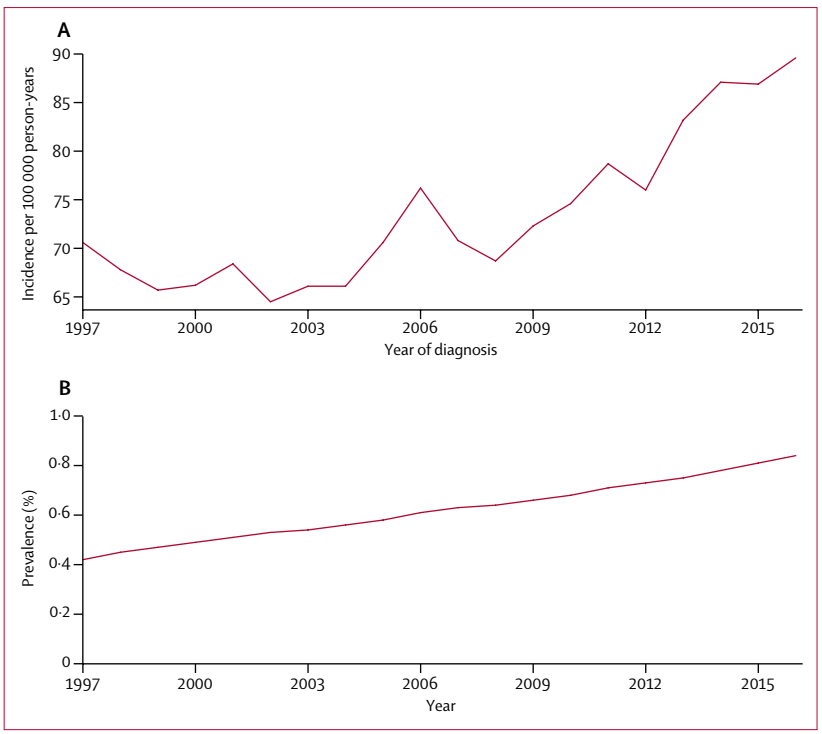


***Figure 2:*** **Epidemiology of cirrhosis in Ontario, Canada, in 1997–2016**
(A) Age-adjusted incidence standardised to the 1991 population. (B) Age-adjusted prevalence standardised to the 1991 population.

## Discussion

In this retrospective population-based study we show that, over the past 20 years, cirrhosis incidence in Canada has increased, with almost 1% of the Ontario population having cirrhosis in 2016. Importantly, this increase in cirrhosis disease burden disproportionally affects younger birth cohorts and women. Given the substantial birth-cohort effects, these findings suggest that these differences are mostly due to changes in chronic liver disease prevalence specific to each birth cohort. To our knowledge, this is the first study to describe the incidence of cirrhosis using an age-period cohort approach.

A cohort effect occurs when different distributions of disease arise from changing disease prevalence or new environmental exposures affecting age groups differently. The causes of chronic liver disease leading to cirrhosis in North America have changed over the past century. In the early 1900s, the most common cause of cirrhosis was alcohol related.[25] In recent decades, hepatitis C infection has become the leading cause for both cirrhosis and liver

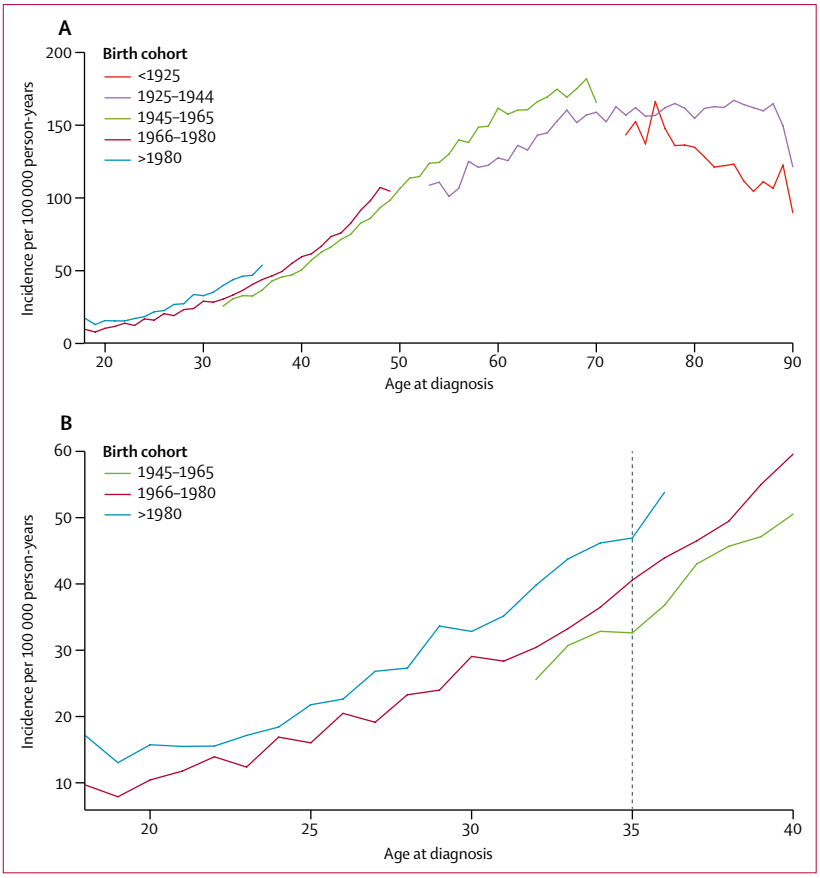


*Figure 3:* **Age-specific and birth-cohort-specific incidence of cirrhosis in Ontario, Canada, in 1997–2016**
(A) Entire cohort. (B) Individuals diagnosed with cirrhosis under the age of 40 years.

| | Overall | Men | Women |
|---|---|---|---|
| **Cirrhosis incidence at age 35** | | | |
| Baby-boomers (1945–65) | 32·6 (28·7–36·5) | 36·3 (30·5–42·0) | 28·9 (23·7–34·1) |
| Generation X (1966–79) | 40·5 (38·1–43·1) | 47·2 (43·4–51·0) | 34·1 (30·9–37·3) |
| Millennials (1980 or later) | 46·9 (39·9–53·9) | 54·5 (43·7–65·3) | 39·7 (30·7–48·7) |
| **Cirrhosis incidence at age 60** | | | |
| Silent generation (1925–44) | 127·7 (119·9–135·2) | 162·3 (150·0–174·6) | 94·1 (84·9–103·3) |
| Baby-boomers (1945–65) | 161·7 (156·0–167·4) | 203·6 (194·4–212·8) | 121·8 (114·8–128·7) |
| **Cirrhosis incidence at age 80** | | | |
| Greatest generation (before 1925) | 134·8 (123·1–146·4) | 165·4 (144·9–186·0) | 114·9 (101·1–128·7) |
| Silent generation (1925–44) | 154·7 (145·8–163·7) | 204·4 (188·7–220·2) | 117·3 (107·0–127·6) |

Data are incidence (95% CI).

*Table 2:* **Age-specific incidence of cirrhosis per 100 000 person-years, by birth cohort**

transplantation in the USA.[26] However, with the emergence of highly effective direct-acting antiviral therapy for hepatitis C, declines in liver-related complications have already been shown.[27,28] Attention has recently turned to the epidemic of NAFLD. First described in 1980,[29] NAFLD is present in 20–30% of the general population[30,31] and approximately 20% of these cases will have the more severe form of disease, non-alcoholic steatohepatitis, and be at risk of progression to cirrhosis.[32] Given the changing epidemiology of chronic liver disease, it is possible that the increase in cirrhosis burden we observed in younger cohorts is in part a result of NAFLD. This is supported by our results showing that most individuals in the millennial birth cohort had cirrhosis with a NAFLD or cryptogenic cause. Further, based on data from the Public Health Agency of Canada, the prevalence of diabetes in 2011 was 6·3% and ranged from 0·7% in individuals aged 20–24 years to 7·0% in individuals aged 45–49 years.[33] The prevalence of diabetes was 9·8% in our millennial cohort and 19·8% in generation X. This difference suggests that our cohorts comprise patients who would be more predisposed to NAFLD than the general population. The prevalence of diabetes[34] and obesity[35] are well documented to parallel cirrhosis trends observed in the generation X and millennial birth cohorts, and both diabetes and obesity have been associated with NAFLD. As the development of cirrhosis from chronic liver disease occurs over a 10–20 year period, the cause for the increase in younger birth cohorts would need to be present in childhood and adolescence. Unlike alcohol and hepatitis C infection, which are mostly limited to the adult population, NAFLD is the most common cause of chronic liver disease in children in industrialised countries.[5,36–38] Previous studies have shown that more than 50% of paediatric patients with NAFLD have at least some degree of hepatic fibrosis at baseline liver biopsy at an average age of 11–13 years,[39,40] and therefore progression to cirrhosis by age 20–30 years is possible. Furthermore, our results are consistent with other studies showing an increase in both the prevalence of chronic liver disease and liver transplantation in adolescents and young adults due to NAFLD[8,10] and the prevalence of non-alcoholic steatohepatitis cirrhosis in the general population.[41]

In addition to NAFLD, alcohol-related liver disease is likely to be a contributing factor to the incidence of cirrhosis in our study population. The Canadian Alcohol and Drug Use Monitoring Survey is an ongoing population-based survey of alcohol and illicit drug use among Canadians aged at least 15 years, which was launched in 2008. The most recent report (from 2012) suggests that those aged 20–29 years had the highest percentage risky alcohol behaviours,[42] and similar trends have also been seen in the USA.[43] Hepatitis C infection might also contribute to the increased cirrhosis disease burden in young adults. Studies from both Canada and the USA have shown that the incidence of hepatitis C infection is increasing in young injection drug users.[44–46] However, because the prevalence of hepatitis C in the general population is ten times lower than that of NAFLD, its contribution to the prevalence of cirrhosis is likely to be to less than that of NAFLD.

There is a paucity of data on the epidemiology of cirrhosis in women. Historically, cirrhosis is considered a predominantly male disease, and most of the few studies

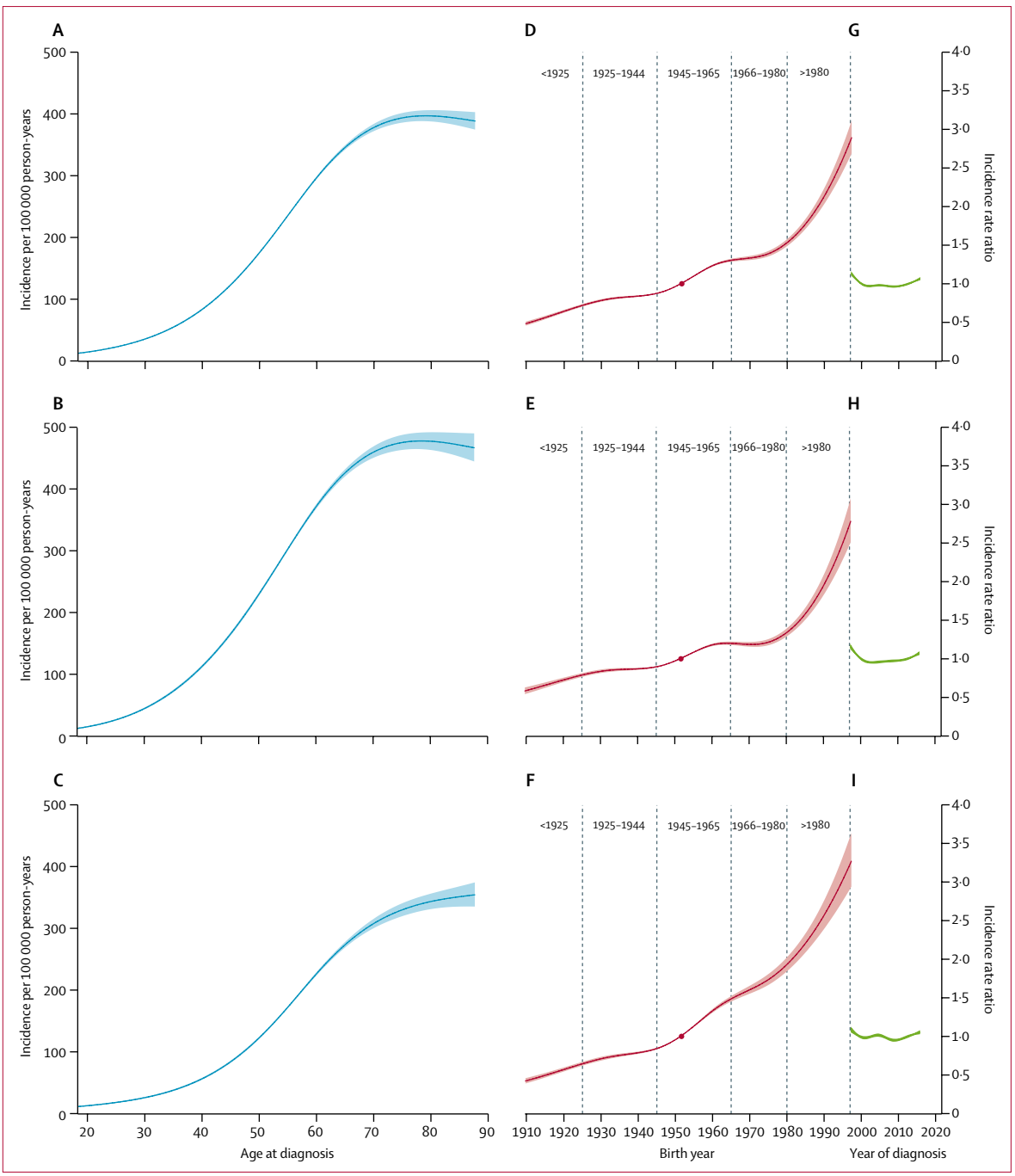


***Figure 4:*** **Age-period-cohort models of cirrhosis incidence in Ontario, Canada, in 1997–2016**
Estimated effect of age on cirrhosis incidence per 100 000 person-years in the overall population (A), men (B), and women (C; shaded area is the 95% CI). Estimated birth-cohort effect on cirrhosis incidence in the overall population (D), men (E), and women (F; circle is the reference year of 1951, shaded area is the 95% CI). Estimated effect of period on cirrhosis incidence in the overall population (G), men (H), and women (I). Overall n=165 979, men n=98 923, women n=67 056.

that have described cirrhosis epidemiology have been limited to men.[12,47] Indeed, our cohort is comprised mostly of men; however, we have shown that there are epidemiological differences between the sexes because the incidence of cirrhosis is increasing faster in women. In the millennial birth cohort, the proportion of men and women with cirrhosis is almost equal, whereas men comprise almost two-thirds of cases in the baby-boomer generation. The reason for this is not immediately apparent, but it is plausible that risk factors for cirrhosis are becoming more equally distributed between sexes. The epidemiology of NAFLD in Canada has not yet been

| | All | Men | Women |
|---|---|---|---|
| 1925 | 0·73 (0·71–0·74) | 0·79 (0·77–0·82) | 0·65 (0·63–0·68) |
| 1945 | 0·88 (0·87–0·89) | 0·90 (0·89–0·91) | 0·85 (0·84–0·86) |
| 1966 | 1·31 (1·29–1·33) | 1·20 (1·17–1·22) | 1·52 (1·48–1·56) |
| 1980 | 1·55 (1·50–1·59) | 1·35 (1·30–1·40) | 1·95 (1·86–2·04) |
| 1990 | 2·16 (2·06–2·27) | 1·98 (1·85–2·12) | 2·60 (2·41–2·79) |

Data represent incidence rate ratios (95% CI) compared with the median birth year (1951). p<0·0001 for all comparison of birth year.

***Table 3:*** **Age-period-cohort analysis describing birth-cohort effects on cirrhosis incidence**

characterised. On the basis of our definition of cirrhosis aetiology, the proportion of individuals in the NAFLD or cryptogenic category in the millennial birth cohort was similar between sexes. There have been conflicting data from other countries on the disease burden in men compared with women. Data from NHANES estimated that NAFLD was 2–3 times more common in men than in women;[36] however, a cohort study from Australia suggested that women have a higher prevalence of NAFLD than men,[48] and data from the UK[49] and the USA[9] propose an equal distribution between the sexes. An additional explanation could be an increase in alcohol-related liver disease in women. Women are well documented to be more susceptible than men to alcohol-related liver damage,[50] and the epidemiology of alcohol use between sexes has started to equalise in more recent birth cohorts.[51,52] This trend was also observed in our study—in earlier birth cohorts, the proportion with alcohol-related causes was more than twice as high in men as in with women, but became almost identical in the millennial cohort. Data from the USA support hepatitis C infection as a potential contributor because the prevalence of the infection has doubled in women aged 15–44 years from 2006 to 2014.[53] Similarly, in Ontario, the rate of new hepatitis C infections in women aged 15–19 years increased from 5·8 per 100 000 person-years in 2005 to 14·1 per 100 000 person-years in 2009.[44] In our study, similar to the trends we noted in NAFLD and alcohol-related causes, the proportion of women with viral hepatitis C infection was similar to that of men in the millennial birth cohort. Although autoimmune liver diseases are more common in women, given the rarity of these conditions and insufficient evidence that the epidemiology has changed over time,[54] these conditions are unlikely to explain the increasing incidence of cirrhosis in women.

Our study results should be considered in light of methodological limitations. Our case definition of cirrhosis is based on a validated algorithm of ICD coding from administrative data. Our sensitivity analysis resulted in about a 30% decrease in total incidence and prevalence of cirrhosis; however, the decline was not differential by birth cohort or sex (data not shown). Importantly, the age-period-cohort results overall and stratified by sex were similar (data not shown).

Our calculations are similar to the only other study on the incidence of cirrhosis in North America that used ICD coding.[12] Data from the VA study showed a prevalence of cirrhosis of 1·06% in 2013.[12] This finding is 25% higher than our 2013 prevalence of 0·75% (95% CI 0·75–0·76); however, our study examined the general population, including women, and the VA population is well known to be enriched with risk factors for the development of cirrhosis, including a high prevalence of hepatitis C infection and alcohol consumption. Because cirrhosis can be a silent disease, the increase in the use of non-invasive methods to diagnose cirrhosis (ie, imaging, elastography, or serum analysis) over the past decade or use of ICD coding could, theoretically, lead to differences in disease ascertainment over the study period, resulting in under-reporting of cirrhosis in the early years. Furthermore, because our validation study was from 2006–14,[19] the accuracy for cirrhosis might have been different in the early years of our study. To account for this possible discrepancy, we used age-period-cohort modelling to adjust for differences in cirrhosis diagnosis over time with the period effects. Although we used coding to assign a potential cause of cirrhosis to each individual, the definition of cirrhosis aetiology in clinical practice is more complex. An individual can have two or more different causes of chronic liver disease, which would be difficult to identify using administrative data. Additionally, we do not have access to medication-related data and we were unable to assess drug-induced liver injury, because there is no ICD code for this type of injury. Therefore, causes of cirrhosis could have been misclassified in our study. However, the trends we described (eg, highest burden of viral hepatitis in the baby-boomer birth cohort and greater burden of alcohol-related disease in men than in women) are consistent with what is known about causes of cirrhosis in general. Finally, our data come from a Canadian population and might not represent the epidemiology of cirrhosis outside of North America or where the causes of chronic liver diseases are different, such as in low-income and middle-income countries.

In conclusion, we have shown that the incidence of cirrhosis in the general population in Canada has increased significantly over the past two decades with the most substantial increases observed in younger birth cohorts and in women. The face of chronic liver disease and cirrhosis appear to be changing in North America, and strategies to increase awareness of this silent epidemic in young adults and women are needed. Future studies focusing on defining the cause and natural history of cirrhosis in these groups are essential to inform chronic liver disease prevention and management strategies with a goal to reverse these trends for future generations.

**Contributors**

JAF was involved in the study concept and design, analysis and interpretation of data, drafting of the manuscript, and obtained funding for the research. YD was involved in the study design, statistical analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. JMM and JS were involved in the

interpretation of data and critical revision of the manuscript for important intellectual content. PAG was involved in the study design, interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision. CMB was involved in the interpretation of data, critical revision of the manuscript for important intellectual content, and study supervision.

#### Declaration of interests

JAF reports grants from Southeastern Ontario Academic Medical Association and grants from American Association for the Study of Liver Disease Foundation, during the conduct of the study. All other authors declare no competing interests.

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