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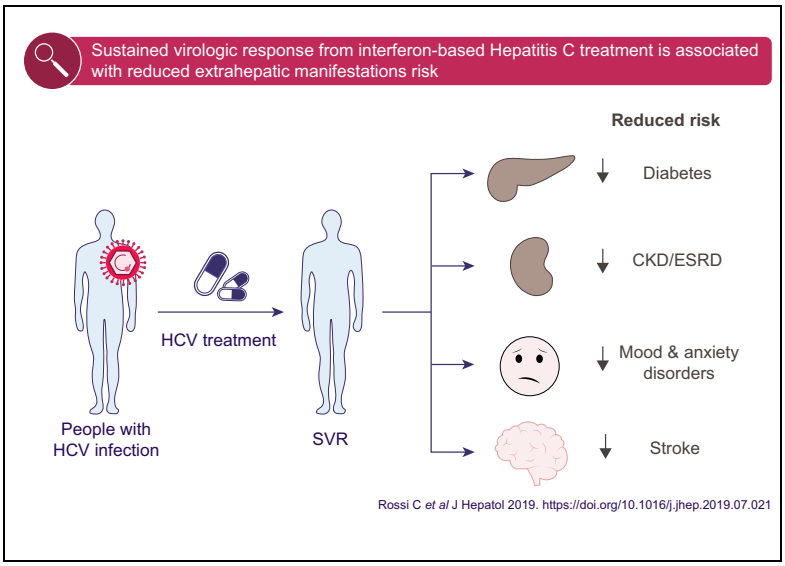
# Sustained virological response from interferon-based hepatitis C regimens is associated with reduced risk of extrahepatic manifestations

## Graphical abstract




## Highlights

- Chronic HCV is associated with many extrahepatic manifestations (EHMs).
- Generalizable population-level estimates of the impact of cure on EHMs are lacking.
- SVR was associated with a significant reduction in the risk of several EHMs.
- Reduction in incidence ranged from 18% (anxiety disorders) to 47% (kidney disease).

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## Lay summary

We estimated the rates of chronic comorbidities other than liver disease between those who were cured and those who failed treatment for hepatitis C virus (HCV) infection. Our findings showed that the rates of these non-liver diseases were largely reduced for those who were cured with interferon-based treatments. Early HCV treatments could provide many benefits in the prevention of various HCV complications beyond liver disease.

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# Sustained virological response from interferon-based hepatitis C regimens is associated with reduced risk of extrahepatic manifestations

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**Background & Aims**: HCV infection is associated with several extrahepatic manifestations (EHMs). We evaluated the impact of sustained virological response (SVR) on the risk of 7 EHMs that contribute to the burden of extrahepatic disease: type 2 diabetes mellitus, chronic kidney disease or end-stage renal disease, stroke, ischemic heart disease, major adverse cardiac events, mood and anxiety disorders, and rheumatoid arthritis.

**Methods**: A longitudinal cohort study was conducted using data from the British Columbia Hepatitis Testers Cohort, which included ~1.3 million individuals screened for HCV. We identified all HCV-infected individuals who were treated with interferon-based therapies between 1999 and 2014. SVR was defined as a negative HCV RNA test ≥24 weeks post-treatment or after end-of-treatment, if unavailable. We computed adjusted subdistribution hazard ratios (asHR) for the effect of SVR on each EHM using competing risk proportional hazard models. Subgroup analyses by birth cohort, sex, injection drug exposure and genotype were also performed.

**Results**: Overall, 10,264 HCV-infected individuals were treated with interferon, of whom 6,023 (59%) achieved SVR. Compared to those that failed treatment, EHM risk was significantly reduced among patients with SVR for type 2 diabetes mellitus (asHR 0.65; 95% CI 0.55–0.77), chronic kidney disease or end-stage renal disease (asHR 0.53; 95% CI 0.43–0.65), ischemic or hemorrhagic stroke (asHR 0.73; 95% CI 0.49–1.09), and mood and anxiety disorders (asHR 0.82; 95% CI 0.71–0.95), but not for ischemic heart disease (asHR 1.23; 95% CI 1.03–1.47), major adverse cardiac events (asHR 0.93; 95% CI 0.79–1.11) or rheumatoid arthritis (asHR 1.09; 95% CI 0.73–1.64).

**Conclusions**: SVR was associated with a reduction in the risk of several EHMs. Increased uptake of antiviral therapy may reduce the growing burden of EHMs in this population.

**Lay summary**: We estimated the rates of chronic comorbidities other than liver disease between those who were cured and those who failed treatment for hepatitis C virus (HCV) infection. Our findings showed that the rates of these non-liver diseases were largely reduced for those who were cured with interferon-based treatments. Early HCV treatments could provide many benefits in the prevention of various HCV complications beyond liver disease.



## Introduction

Chronic HCV infection, which affects more than 71 million people worldwide, is an important source of morbidity and mortality.[1] Although liver-related sequelae have been well characterized, extrahepatic manifestations (EHM) associated with HCV have received considerably less attention.[2–4] These EHMs include metabolic,[5] cardiovascular,[6] renal,[7] autoimmune,[8] lymphoproliferative,[9] and neurologic conditions which are estimated to be present in as many as 31% of HCV-infected individuals.[3,10,11] Direct medical costs associated with EHMs are substantial and range between $72 million and $443 million US dollars per year.[3] Increasing rates of healthcare resource utilization associated with EHMs have also been reported[12,13] and, with a largely aging HCV-infected population, there is a greater need to assess the broader HCV-related disease burden and interventions to reduce future morbidity and mortality.

A sustained virological response (SVR) to HCV treatment has been associated with marked reductions in all-cause and liver-related mortality;[14] however, there are limited data regarding the effect of SVR on the risk of developing EHMs.[15] Initial studies from Asia during the interferon era reported reduced rates of type 2 diabetes mellitus (T2DM),[16] hemorrhagic and ischemic stroke,[17,18] chronic kidney disease (CKD) or end-stage renal disease (ESRD),[18,19] and acute coronary syndrome[18] associated with SVR; however, these studies were limited by the small number of clinical events and incomplete linkages to assess HCV cure. Furthermore, this evidence may not be generalizable

Keywords: Antiviral therapy; Canada; Comorbidity; Epidemiology; Extrahepatic; Hepatitis C virus; Sustained virologic response.
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to HCV-infected populations in North America, who are both younger and more likely to have pre-existing chronic conditions.[20] More recently, a large study from the United States Veterans Affairs clinical cohort has reported a protective association between SVR and subclinical disease, but not for chronic conditions, such as coronary heart disease or stroke, though another study on the same population recently reported a protective effect for cardiovascular diseases compared to untreated individuals.[21–25] As >95% of veterans are male and may experience different risk profiles, these findings may not be generalizable. Additional studies in European patients with specific comorbid conditions, such as HIV coinfection[26] and advanced liver disease,[8,27] have reported reduced rates of certain EHMs among those who achieved SVR. Given the limitations of the existing literature, there is a need for comprehensive assessment of the effect of SVR on various EHMs among the general population.

As fibrosis restrictions for publicly funded treatment are lifted and direct-acting antiviral (DAA) therapies become more widely available, assessments of the broader population-level impact of curative treatment on the development and health system-related costs of EHMs are required.[28] Given EHMs often develop over many years and there is limited data to assess EHM incidence with DAAs, the objective of this study was to measure the association between SVR and the incidence of several clinically important chronic EHMs using long-term follow-up from an administrative-linked, population-based cohort study in British Columbia, Canada, during the interferon era.

## Materials and methods

### Study population

We used data from the British Columbia Hepatitis Testers Cohort (BC-HTC), which includes all individuals (~1.7 million) tested for HCV or HIV at the British Columbia Centre for Disease Control Public Health Laboratory, or reported to public health as a confirmed case of HCV, HBV, HIV, or tuberculosis, since 1990. These data were linked with information on medical visits, hospitalization records, chronic disease registry, prescription drug dispensations, cancer incidence, and mortality (Table S1). Further information about the BC-HTC, including methodology and data linkages has previously been published.[29]

This analysis included all HCV-positive individuals who initiated treatment, identified through pharmacy dispensations, with an interferon-based therapy between April 1st, 1999 and July 1st, 2014, with or without ribavirin or a first-generation DAA. We excluded individuals who died. Individuals who failed their first treatment and were re-treated with interferon were censored at re-treatment in the primary analysis. However, people who were re-treated were included in the sensitivity analysis, where effect of SVR after last treatment was assessed. The linkages between physician visits and hospitalizations were available until December 31st, 2015. To allow sufficient follow-up time for observation of EHMs, only individuals who initiated interferon prior to July 1st, 2014 were included.

Data linkage to establish the BC-HTC was performed under the auspices of the British Columbia Centre for Disease Control's public health mandate. This study was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (H14-01649).

### Case definitions

The primary exposure was SVR, which was assessed at the first HCV RNA measurement ≥24 weeks post-treatment. If this was unavailable, we examined the last measurement between end-of-treatment and 24 weeks post-treatment to assess SVR. Patients were considered to have achieved SVR if HCV RNA was undetectable. Patients with no post-treatment HCV RNA measurements were considered to have failed treatment, and as shown previously,[30] included individuals who had a positive RNA test on treatment who did not return for SVR assessment. HCV RNA testing were performed in accordance with centralized laboratory standards.

We selected 7 chronic EHMs previously identified as major contributors to the HCV-related extrahepatic disease burden in terms of resource utilization and costs.[3,11] These were i) T2DM; ii) CKD or ESRD; iii) cerebrovascular disease (*i.e.* ischemic or hemorrhagic stroke or transient ischemic attack); iv) ischemic heart disease (IHD); v) major adverse cardiac events (MACE), which included acute myocardial infarction, unstable angina, congestive heart failure, peripheral vascular disease, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, and stroke; (vi) mood and anxiety disorders; (vii) rheumatoid arthritis (RA). EHMs were assessed using a combination of international classification of diseases diagnostic or procedure codes, or fee item codes from medical visits, hospital admissions, or the prescription database, as applicable, based on the British Columbia Chronic Disease Registry definitions (Table S2).

We assessed the following confounders, identified *a priori* (Table S3): age, sex, history of injection drug use, problematic alcohol consumption, major mental health illness, quintiles of social and material deprivation, hypertension, statin use, T2DM, HBV and HIV coinfection, last observed HCV genotype, liver cirrhosis, year of HCV diagnosis (1990–1995, 1996–1999, 2000–2003, 2004–2014), and year of HCV treatment initiation (1999–2004, 2005–2009, 2010–2014). Covariates were measured at SVR assessment and were considered time-invariant. T2DM and major mental health illness were not included as covariates in analyses for incident diabetes and mood and anxiety disorders, respectively.

### Statistical analyses

We compared baseline characteristics between those who achieved SVR with interferon-based therapy and those who did not. Each of the 7 study EHMs of interest were then analyzed separately. For each EHM, patients were followed from the date of SVR assessment for both those who achieved or did not achieve SVR (index date) until the earliest of i) date of the incident EHM outcome of interest, ii) HCV re-infection, iii) re-treatment for HCV, iv) death, or v) December 31st, 2015, the last date follow-up data was available. Patients with prevalent diagnoses of EHMs using the same incident definitions were excluded from the analysis of that specific EHM. As a result, each of the 7 EHM analyses contained a different number of patients. Prevalent EHMs were assessed prior to the index date. We calculated EHM incidence rates among those who achieved SVR and those who did not by dividing the number of events by at risk person-years of follow-up (PYFU). Cumulative incidence curves were constructed to estimate the 10-year risk of each EHM among those who achieved SVR and those who did not. Cumulative incidence curves were compared using Gray's K-sample test.[31] We constructed 2 sets of proportional

hazards models accounting for competing mortality risk; a cause-specific model and proportional subdistribution hazards model (Fine-Gray model) to assess the impact of SVR on each EHM. Results from proportional subdistribution hazards model (Fine-Gray model) were presented as primary results. To compare how the hazard ratio (HR) changed with inclusion of various confounders, we included covariates sequentially in separate models. Proportional hazards assumption was assessed and satisfied for all models.[32] We performed stratified analyses to assess whether observed associations differed by birth cohort (1920–1944, 1945–1964, 1965–2000), sex, injection drug use history, HCV genotype and cirrhosis status. In a sensitivity analysis, we restricted our study to only those patients with an available HCV RNA measurement ≥24 weeks post-treatment to assess SVR. In a separate analysis, we also excluded events occurring within 6 months after SVR. All analyses were performed using SAS 9.4 (Cary, North Carolina).

## Results

Between April 1st, 1999 and July 1st, 2014, 10,264 HCV-infected individuals had initiated treatment with interferon-based therapies and were alive and not re-treated within 24 weeks after the end of the first interferon-based course of therapy (Fig. 1). HCV RNA measurements ≥24 weeks post-treatment were available for 9,013 individuals (88%) and 505 (5%) were tested between end-of-treatment and 24 weeks post-treatment. The remainder were not tested post-treatment. A total of 6,023 patients achieved SVR (59%). Of 505 tested between end-of-treatment and 24 weeks post-treatment, 353 (69.9%) had a negative RNA test. Among those testing negative, 224 (63%) had an RNA test >12 weeks after treatment.

Most interferon-treated individuals were male (68%) and were born between 1945 and 1964 (72%; median age 51 years; interquartile range, 44–56). History of injection drug use was reported in 21% of patients. Patients who were significantly more likely to have failed treatment were: males, individuals born between 1945–1964, those with problematic alcohol consumption, hypertension, diabetes, HIV/HBV coinfection, HCV genotype 1 or liver cirrhosis, as well as those treated between 1999–2004, diagnosed before 1995, and treated without pegylated-interferon (Table 1).

The prevalence of EHMs prior to the index date ranged from 0.7% for hemorrhagic or ischemic stroke to 61% for mood and anxiety disorders. Final sample sizes for each of the incident EHM-specific analyses are shown in Fig. 1. In order of increasing incidence, we observed the following overall EHM incidence rates (per 1,000 PYFU): 1.7 for stroke and RA, 6.6 for CKD or ESRD, 9.3 for IHD, 9.6 for T2DM, 9.8 for MACE and 35.7 for mood and anxiety disorders. With the exception of RA, all EHM incidence rates were higher among patients who failed to achieve SVR (Table S4). Depending on the outcome, the median follow-up time ranged from 6.0 years to 7.0 years among those who achieved SVR and ranged from 4.6 years to 5.9 years among those failed to achieve SVR.

### Cumulative incidence

The cumulative incidences of the 7 EHMs are shown in Fig. 2. The 10-year cumulative incidences of T2DM (Fig. 2A), CKD or ESRD (Fig. 2B), ischemic or hemorrhagic stroke (Fig. 2C), MACE (Fig. 2E), and mood anxiety disorders (Fig. 2F) were all significantly lower among those who achieved SVR than those who failed treatment: 6.8% (95% CI 6.0%–7.7%) *vs.* 11.8% (95% CI 10.6%–13.2%) for T2DM ($p$ <0.0001), 3.8% (95% CI 3.2%–4.5%) *vs.* 9.6% (95% CI 8.4%–10.8%) for CKD or ESRD ($p$ <0.0001), 1.2% (95% CI 0.8%–1.6%) *vs.* 2.2% (95% CI 1.6%–2.8%) for ischemic or hemorrhagic stroke ($p$ = 0.003), 8.3% (95% CI 7.3%–9.2%) *vs.* 10.5% (95% CI 9.3%–11.8% for MACE ($p$ = 0.0002), and 25.3% (95% CI 23.2%–27.4%) *vs.* 30.0% (95% CI 27.3%–32.8%) for mood and anxiety disorders ($p$ = 0.004), respectively. Conversely, there were no differences in the cumulative incidences of IHD (Fig. 2D) or RA (Fig. 2G) between the SVR and non-SVR groups:

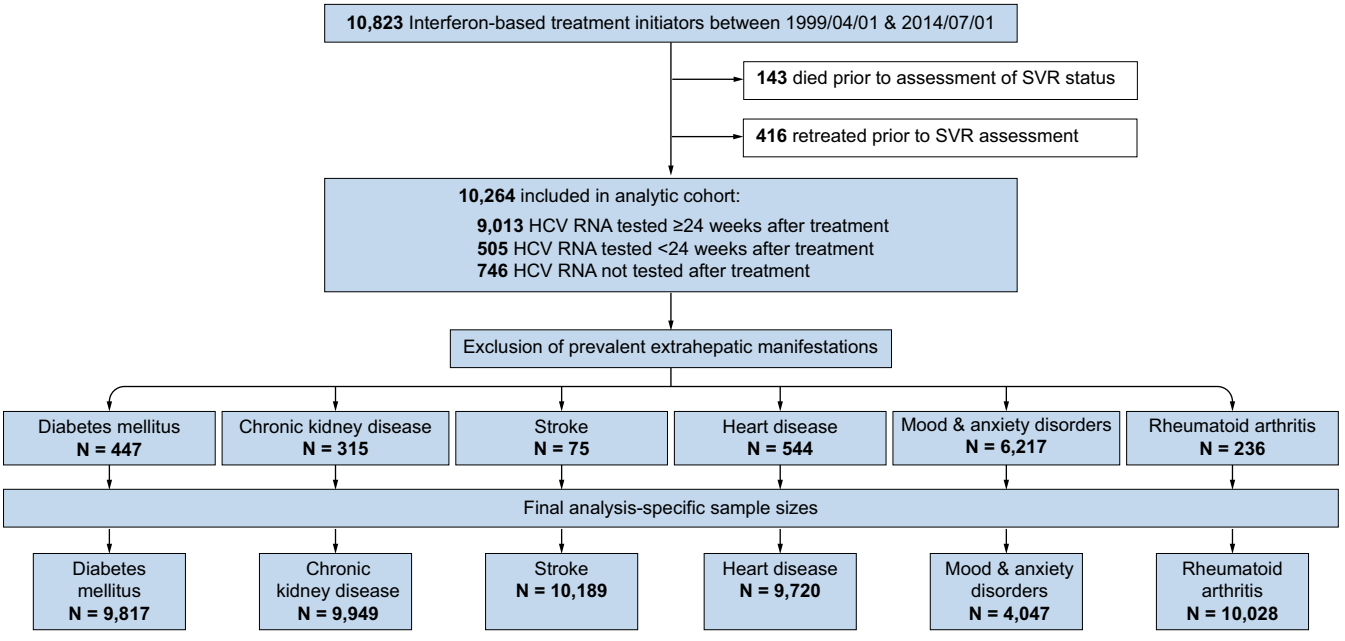


**Fig. 1. Study inclusion flow chart**. SVR, sustained virological response.

**Table 1. Baseline characteristics of participants with and without SVR between 1999 and 2014.**

| | Overall (n = 10,264) | SVR (n = 6,023) | Failed to achieve SVR (n = 4,241) | *p* value[†] |
|---|---|---|---|---|
| Median age at SVR assessment (IQR), years | 51 (44–56) | 50 (43–56) | 51 (45–57) | <0.0001 |
| Birth cohort | | | | <0.0001 |
| 1920–1944 | 654 (6%) | 324 (5%) | 330 (8%) | |
| 1945–1964 | 7,388 (72%) | 4,127 (69%) | 3,261 (77%) | |
| 1965–2000 | 2,222 (22%) | 1,572 (26%) | 650 (15%) | |
| Male sex | 6,932 (68%) | 3,973 (66%) | 2,953 (70%) | 0.0001 |
| Injection drug use | 2,158 (21%) | 1,261 (21%) | 897 (21%) | 0.79 |
| Problematic alcohol use | 1,994 (19%) | 1,123 (19%) | 871 (21%) | 0.02 |
| Major mental illness | 2,584 (25%) | 1,488 (25%) | 1,096 (26%) | 0.19 |
| Hypertension | 1,970 (19%) | 1,103 (18%) | 867 (20%) | 0.007 |
| Diabetes | 447 (4%) | 192 (3%) | 255 (6%) | <0.0001 |
| Statin use | 577 (6%) | 369 (6%) | 208 (5%) | 0.008 |
| HBV coinfection | 504 (5%) | 257 (4%) | 247 (6%) | 0.0003 |
| HIV coinfection | 479 (5%) | 255 (4%) | 224 (5%) | 0.01 |
| Liver cirrhosis | 593 (6%) | 204 (3%) | 389 (9%) | <0.0001 |
| Last observed HCV genotype | | | | <0.0001 |
| GT1 | 5,059 (49%) | 2,468 (41%) | 2,591 (61%) | |
| GT2 | 1,469 (14%) | 1,125 (19%) | 344 (8%) | |
| GT3 | 2,592 (25%) | 1,741 (29%) | 851 (20%) | |
| Other/Mixed | 165 (2%) | 106 (2%) | 59 (1%) | |
| Unknown | 979 (10%) | 583 (10%) | 396 (9%) | |
| Year of HCV diagnosis | | | | <0.0001 |
| 1990–1995 | 1,304 (13%) | 689 (11%) | 615 (15%) | |
| 1996–1999 | 2,980 (29%) | 1,620 (27%) | 1,360 (32%) | |
| 2000–2003 | 2,636 (26%) | 1,477 (25%) | 1,159 (27%) | |
| 2004–2014 | 3,344 (32%) | 2,237 (37%) | 1,107 (26%) | |
| Material deprivation quintiles | | | | 0.68 |
| 1 (most privileged) | 1,428 (14%) | 820 (14%) | 608 (14%) | |
| 2 | 1,678 (16%) | 980 (16%) | 698 (16%) | |
| 3 | 1,946 (19%) | 1,134 (19%) | 812 (19%) | |
| 4 | 2,235 (22%) | 1,325 (22%) | 910 (21%) | |
| 5 (most deprived) | 2,713 (26%) | 1,616 (27%) | 1,097 (26%) | |
| Missing | 264 (3%) | 148 (2%) | 116 (3%) | |
| Social deprivation quintiles | | | | 0.05 |
| 1 (most privileged) | 1,335 (13%) | 818 (14%) | 517 (12%) | |
| 2 | 1,514 (15%) | 898 (15%) | 616 (15%) | |
| 3 | 1,805 (18%) | 1,048 (17%) | 757 (18%) | |
| 4 | 2,161 (21%) | 1,297 (22%) | 864 (20%) | |
| 5 (most deprived) | 3,185 (31%) | 1,814 (30%) | 1,371 (32%) | |
| Missing | 264 (3%) | 148 (2%) | 116 (3%) | |
| Year of HCV treatment initiation | | | | <0.0001 |
| 1999–2004 | 3,672 (36%) | 1,817 (30%) | 1,855 (44%) | |
| 2005–2009 | 3,802 (37%) | 2,323 (39%) | 1,479 (35%) | |
| 2010–2014 | 2,790 (27%) | 1,883 (31%) | 907 (21%) | |
| Treatment category | | | | <0.0001 |
| Interferon monotherapy | 756 (7%) | 365 (6%) | 391 (9%) | |
| Interferon–ribavirin | 1,353 (13%) | 571 (9%) | 782 (18%) | |
| Pegylated interferon–ribavirin | 7,325 (71%) | 4,489 (75%) | 2,836 (67%) | |
| Pegylated interferon–ribavirin–protease inhibitor | 830 (8%) | 598 (10%) | 232 (5%) | |

GT, genotype; IQR, interquartile range; SVR, sustained virological response.
[†] Continuous variables were compared using the non-parametric Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test.

8.6% (95% CI 7.6%–9.6%) *vs.* 8.9% (95% CI 7.8%–10.1%) for IHD ($p = 0.78$) and 1.4% (95% CI 1.0%–1.8%) *vs.* 1.3% (95% CI 0.9%–1.7%) for RA ($p = 0.44$), respectively.

### Multivariable analyses

In competing risk subdistribution proportional hazards model, after adjusting for confounders, the association between achieving SVR and the reduced risk of T2DM, CKD or ESRD, ischemic or hemorrhagic stroke, and mood and anxiety disorders remained significant (Table 2). Successful treatment was associated with an adjusted subdistribution hazard ratio (asHR) of 0.65 (95% CI 0.55–0.77) for T2DM, 0.53 (95% CI 0.43–0.65) for CKD or ESRD, 0.73 (95% CI 0.49–1.09) for stroke, and 0.82 (95% CI 0.71–0.95) for mood and anxiety disorders, respectively. In contrast, SVR was not associated with a reduction in the risk of IHD (asHR 1.23; 95% CI 1.03–1.47), MACE (asHR 0.88; 95% CI 0.74–1.05) or RA (asHR 1.09; 95% CI 0.73–1.64). Results from the multivariable analyses were largely consistent with the cause-specific model (Table S7), when we restricted our study to those with HCV RNA ≥24 weeks post-treatment to assess SVR (Table S5), excluded events occurring <180 days after SVR to reduce the possibility of lead time bias (Table S8), and used last treatment instead of first treatment (Table S6). Notable differences include significant reductions in MACE risk using all treated individuals with SVR from last treatment and the cause-specific model.

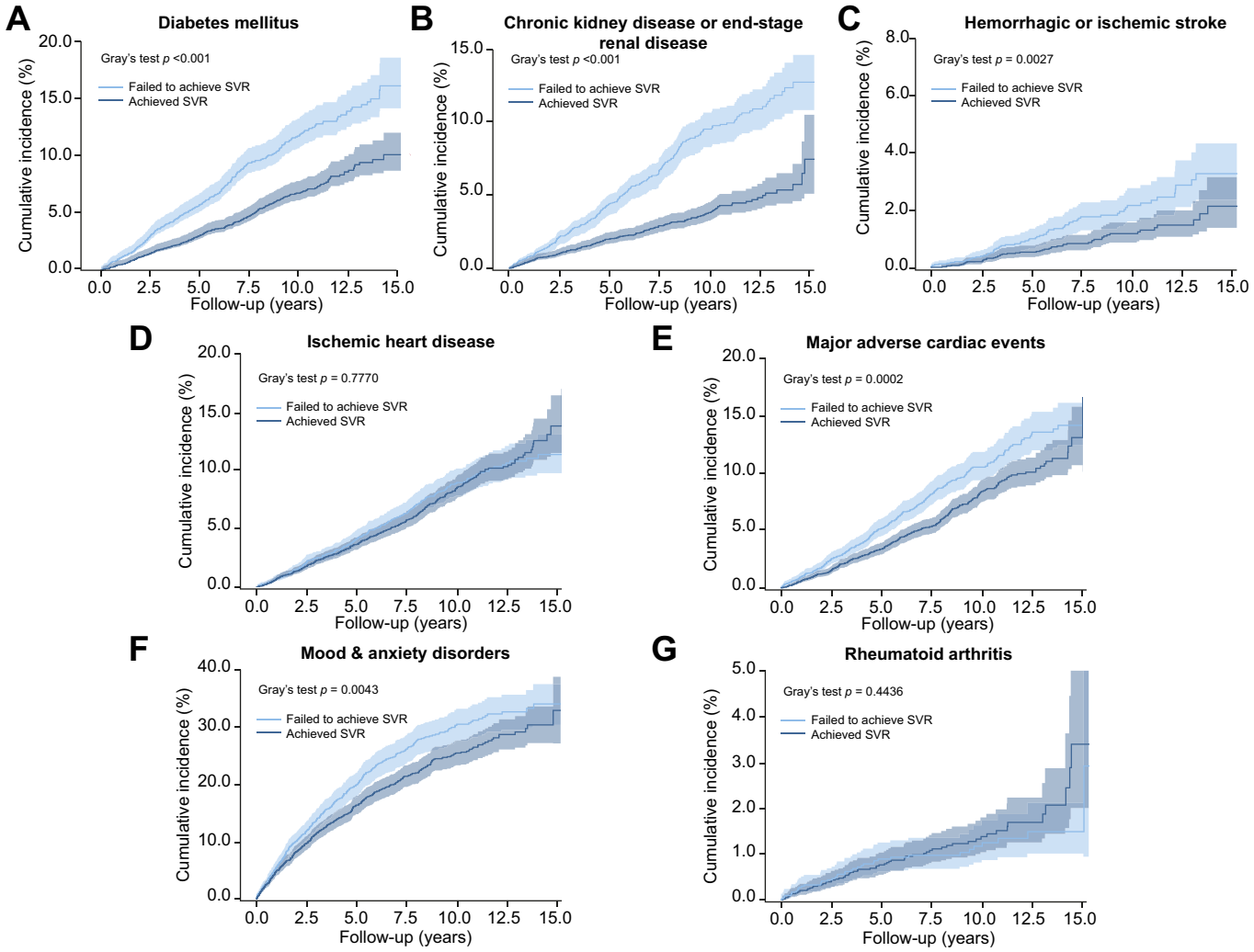


**Fig. 2. Cumulative Incidence of extrahepatic manifestations between SVR and non-SVR patients.** (A) Diabetes mellitus. (B) Chronic kidney or end-stage renal disease. (C) Ischemic or hemorrhagic stroke. (D) Ischemic heart disease. (E) Major adverse cardiac events. (F) Mood and anxiety disorders. (G) Rheumatoid arthritis. SVR, sustained virological response.
Cumulative incidence functions (CIF) were compared using Gray's K-sample test.

**Table 2. Effect of SVR on incident extrahepatic manifestations using proportional hazards model accounting for competing mortality risk, according to covariate adjustment.**[†]

| | | | Adjusted subdistribution hazard ratios (95% CI) | | |
|---|---|---|---|---|---|
| | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
| Diabetes | 0.60 (0.51–0.70) | 0.60 (0.51–0.70) | 0.58 (0.50–0.68) | 0.66 (0.56–0.78) | 0.65 (0.55–0.77) |
| Chronic kidney disease or end-stage renal disease | 0.46 (0.38–0.56) | 0.46 (0.38–0.56) | 0.48 (0.39–0.58) | 0.50 (0.41–0.62) | 0.53 (0.43–0.65) |
| Ischemic or hemorrhagic stroke | 0.64 (0.45–0.92) | 0.64 (0.44–0.93) | 0.68 (0.47–0.98) | 0.71 (0.48–1.04) | 0.73 (0.49–1.09) |
| Ischemic heart disease | 1.08 (0.92–1.28) | 1.10 (0.93–1.30) | 1.08 (0.92–1.28) | 1.20 (1.01–1.43) | 1.23 (1.03–1.47) |
| Major adverse cardiac events | 0.83 (0.71–0.98) | 0.85 (0.72–0.99) | 0.85 (0.73–1.0) | 0.90 (0.76–1.06) | 0.93 (0.79–1.11) |
| Mood and anxiety disorders | 0.78 (0.68–0.89) | 0.81 (0.71–0.93) | 0.78 (0.68–0.90) | 0.80 (0.69–0.92) | 0.82 (0.71–0.95) |
| Rheumatoid arthritis | 1.11 (0.74–1.66) | 1.11 (0.74–1.66) | 1.07 (0.71–1.59) | 1.14 (0.76–1.71) | 1.09 (0.73–1.64) |

SVR, sustained virological response.
[†] Model 1 was adjusted for age (linear term) and sex. Model 2 was adjusted for age, sex, injection drug use, problematic alcohol consumption, mental health [except for mood and anxiety disorders outcome] and social and material deprivation quintiles. Model 3 was adjusted for age, sex, HBV and HIV coinfection, statin use, hypertension, and diabetes (except for diabetes outcome). Model 4 was adjusted for age, sex, HCV genotype, year of HCV treatment initiation, year of HCV diagnosis and liver cirrhosis. Model 5 was adjusted for all covariates included in Models 2 through 4.

### Stratified analyses

The association between SVR and the reduction of T2DM, CKD or ESRD, stroke, and mood and anxiety disorders were, overall, consistent across strata defined by birth cohort, gender, injection drug use history, and HCV genotype (Fig. 3). Notably, however, SVR was associated with greater reduction in risk for diabetes, CKD/ESRD, stroke, MACE and mood and anxiety disorders among those without cirrhosis compared to those with cirrhosis. SVR was also associated with larger protective effect for CKD or ESRD in females (asHR 0.39; 95% CI 0.28–0.56; Fig. 3B)

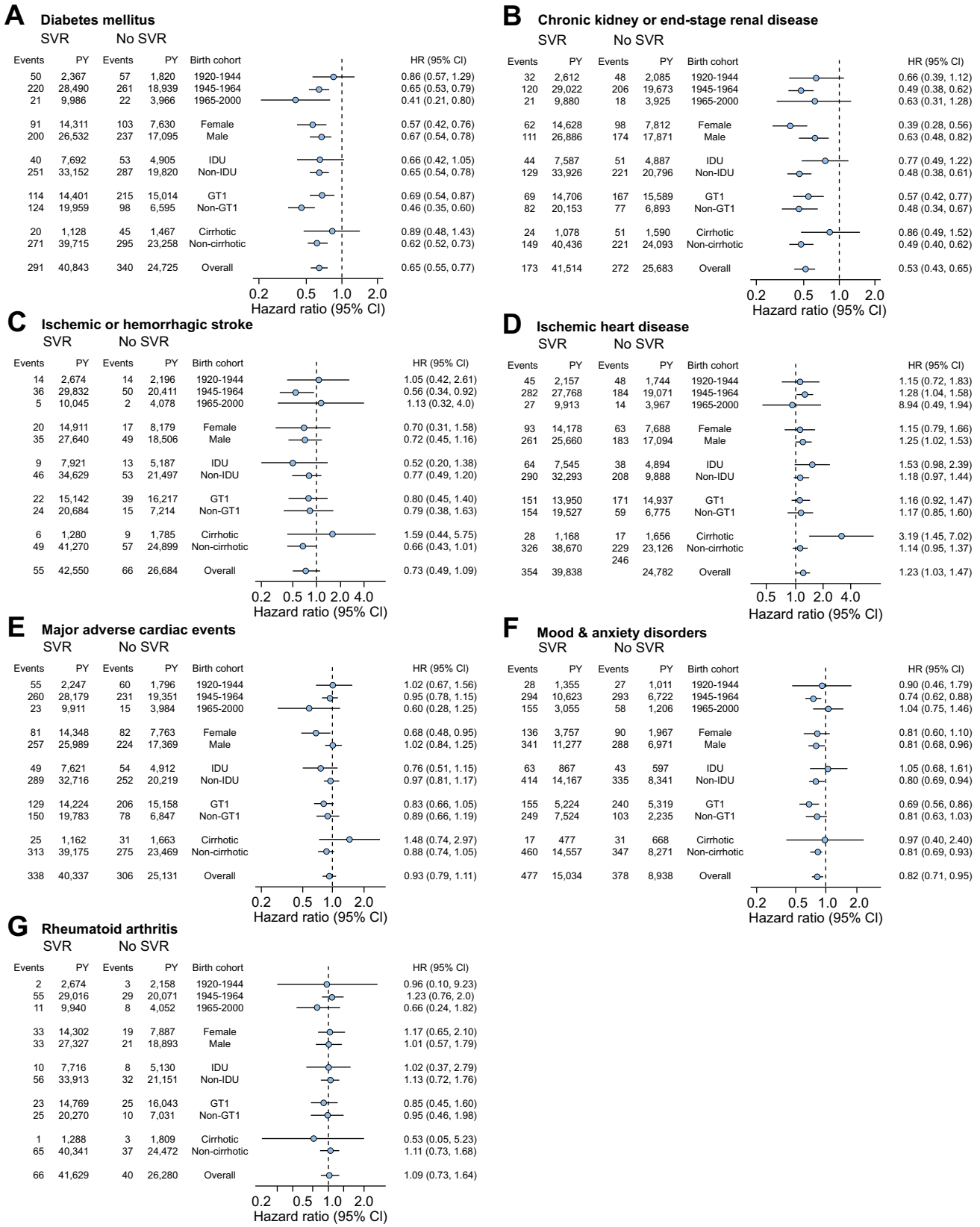


**Fig. 3. Multivariable-adjusted analyses stratified by birth cohort, gender, injection drug use, and HCV genotype**. (A) Diabetes mellitus. (B) Chronic kidney or end-stage renal disease. (C) Ischemic or hemorrhagic stroke. (D) Ischemic heart disease. (E) Major adverse cardiac events. (F) Mood and anxiety disorders. (G) Rheumatoid arthritis. PY, person-years; SVR, sustained virological response.

compared to males (asHR 0.63; 95% CI 0.48–0.82), among those with no history of IDU (asHR 0.48; 95% CI 0.38–61) compared to those with a history of IDU (asHR 0.77; 95% CI 0.49–1.22). SVR was also associated with a higher reduction in risk of MACE in females (asHR 0.68; 95% CI 0.48–0.95) compared to males (asHR 1.02; 95% CI 0.84–1.25). In addition, achieving SVR was also associated with a larger reduction in the risk of stroke among those born between 1945 and 1964 (asHR 0.50; 95% CI 0.31–0.80; Fig. 3C), and risk of diabetes among people born between 1965–2000 (asHR 0.41; 95% CI 0.21–0.80; Fig. 3A). SVR was not associated with a reduction of IHD or RA incidence in any of the stratified analyses. SVR was associated with a greater reduction in CKD/ESRD risk among those without diabetes (asHR 0.51; 95% CI 0.41–0.63) compared to those with diabetes (asHR 0.82; 95% CI 0.45–1.49).

## Discussion

In this large, population-based cohort of 10,264 HCV-infected patients who initiated treatment with interferon-based therapies, we observed a reduction in the incidence of several EHMs. The cumulative incidence of T2DM, CKD or ESRD, ischemic or hemorrhagic stroke, and mood and anxiety disorders were all significantly lower in patients who achieved SVR, compared to those who failed interferon therapy. After accounting for potential confounding factors, these associations remained significant. The relative reduction in EHM incidence for these outcomes was large and ranged from 18% for mood and anxiety disorders to 47% for CKD or ESRD. The effect of MACE reduction was more pronounced among women. Overall, these findings support the extrahepatic benefit of achieving SVR and extend previous findings that have demonstrated reduced subclinical illness and mortality associated with HCV viral eradication.[15,33,34]

Previous studies reported associations between chronic HCV infection and metabolic manifestations, including insulin resistance and T2DM.[5,35,36] Consistent with earlier work from Japan,[16] cohorts from the United States,[21,24,25] and the Spanish HCV-HIV coinfection cohort,[26] our results support these findings, as we have demonstrated that HCV cure with antiviral therapy results in a reduction in the incidence of T2DM in our population. Recent debate regarding the mechanism underlying HCV-induced T2DM may impact clinical care for patients treated for chronic HCV.[37,38] Although HCV can directly activate inhibitors of insulin signaling pathways, recent evidence suggests HCV or fatty liver-induced inflammation, which may also interfere with transduction pathways, could be responsible for this observed association.[37] As a result, viral eradication alone may not reduce the excess T2DM risk associated with HCV and further monitoring of liver enzymes and assessment of fatty liver disease risk factors may be warranted.

Successful HCV treatment has been associated with improvements in symptoms related to type II mixed cryoglobulinemia vasculitis[39] and membranoproliferative glomerulonephritis.[40] Typically, these studies examined markers of kidney disease, which include serum cryoglobulins, urinary proteinuria, and kidney function. However, there is limited data on the impact of viral clearance on the incidence of CKD or ESRD.[2,15] Analysis of administrative data from national claims databases in Taiwan[18,41] and the United States[7] showed that interferon therapy was associated with a large reduction in the incidence of ESRD and CKD, respectively, however, these studies lacked laboratory data to assess SVR and were limited to comparisons between treated and untreated HCV-infected patients. This may have introduced indication bias in these analyses, as patients with HCV and comorbid conditions that may be associated with ESRD, for example, may not have been eligible to receive interferon. Thus, the effect of treatment may have been overestimated. This may explain the 85% reduction in the rate of ESRD associated with interferon therapy in Taiwan.[18] In our analyses, we observed a 47% reduction in incident CKD or ESRD associated with SVR, which was comparable to other studies that have reported reductions between 25% and 63% when comparing SVR and non-SVR patients in the interferon era.[19,25,26] These studies have included both largely cirrhotic patients and those coinfected with HIV, and thus it is reassuring to observe an extrahepatic benefit of SVR in populations that traditionally experience poorer clinical outcomes.

HCV has been associated with increased cerebrovascular disease-related mortality, particularly among patients with diabetes or hypertension.[6,42] Studies of vascular abnormalities identified increased intima-media thickness and a greater risk of developing atherosclerosis in HCV-infected individuals, compared to HCV seronegative individuals,[43,44] which may result in carotid stenosis and an overall increased risk of cerebrovascular disease. A recent analysis reported an improvement in intima-media thickness and carotid thickening in both cirrhotic and non-cirrhotic patients cured with DAAs 1-year post-treatment.[45] Our results support these findings, demonstrating a long-term extrahepatic benefit in terms of both ischemic and hemorrhagic stroke. However, the overall incidence rate of stroke in our analysis (1.7 per 1,000 PYFU) was smaller than the rate reported in an analysis of United States' veterans (10 per 1,000 PYFU). These differences in rates are largely reflective of the additional comorbidities experienced by veterans, who had a high prevalence of obesity, smoking, hypertension and advanced fibrosis.[25] In contrast, the 27% observed reduction in the risk of stroke associated with SVR was slightly lower than studies from Asia which reported reductions ranging from 38% to 69%.[17,18,46] The association of SVR with other cardiac events including IHD and MACE is not consistent. Many studies from the interferon-era did not find a significant reduction in the risk of cardiac events with SVR, while others including those from the DAA era did.[8,22,25] We did not observe a significant reduction in the risk of MACE with SVR in the overall study population of treatment naïve individuals, after adjusting for confounders. However, there was a significant reduction in the risk of MACE among females. In addition, there was a significant reduction in MACE risk using all treated individuals, as well as using the cause-specific model. Risk reduction was higher among those without cirrhosis. In a study by Butt *et al.*, DAA treatment was associated with a reduction in the risk of overall cardiac events, but SVR was not associated with a reduction in the risk of specific cardiac events.[22] Similarly, a significant reduction in MACE risk was reported in people with cirrhosis in a study from France.[8] Differences in results could be related to study methodology (many studies did not account for competing mortality risk), study population, or treatment type and comparison group.[22,25] Use of an untreated group as a comparison is complicated by confounding by indication, as well as lack of comparability of index date for follow-up. Further studies are needed, using rigorous methodology to account for confounding by indication, competing risk, and comparable follow-up start time.

One important finding of this study was the high incidence rate of mood and anxiety disorders (36 per 1,000 PYFU) among

HCV-infected individuals in our population. An emerging body of knowledge considers HCV as part of a larger syndemic that includes broader social and structural determinants of health that increase the risk of viral acquisition and promote poorer long-term clinical outcomes.[47–49] Although we observed a 18% reduction in the relative risk of mood and anxiety disorders associated with viral clearance, it is not surprising to still observe elevated rates of mental health-related diagnoses among individuals who achieved SVR. The same structural factors that increase the likelihood of becoming infected, such as neighborhood-level social capital, stigma, and access to health services, are also related to homelessness, food insecurity, risk behaviors, substance use and mental health disorders.[50] In light of this syndemic model, HCV treatment should be incorporated into larger, integrative models of care that include not only medical care but improved access to services in demand by the community, including harm reduction, food banks, subsidized housing, and employment/placement agencies. Our study adds to the existing body of knowledge demonstrating an impact of SVR from both interferon and DAA-based therapies on reducing fatigue and improving health-related quality of life and neurocognitive function.[51,52] However, as far as we can tell, this is the first study to report a reduction in the incidence of diagnosed mood and anxiety disorders, including depression, associated with successful HCV treatment. However, since mood and anxiety disorders may be affected by ascertainment issues, caution is needed when interpreting these findings. Further studies are needed to confirm our findings.

Our overall findings have important clinical and population health-level implications. With the availability of highly effective DAAs (>95% SVR), which are well-tolerated, have few contraindications and produce minimal side effects, there is little reason to restrict access for these medications to only those with advanced fibrosis or cirrhosis. We, along with others,[25] have demonstrated that SVR produces important benefits that extend beyond the liver and reduce extrahepatic morbidity and mortality in the chronic HCV-infected population, independent of liver disease severity. Successful HCV treatment may not only reduce the incidence of EHMs, but also reduce healthcare resource utilization associated with these long-term chronic conditions. Several studies estimated large direct medical costs associated with EHMs[3,10,11] and that these costs have been increasing among patients with longer durations of infection. As a result, expansion of DAA therapy to all chronic HCV-infected patients may be a valuable intervention to reduce the medical costs of EHMs. Previous economic evaluations of these new DAAs have not incorporated direct and indirect costs related to EHMs in assessing whether these treatments are cost-effective and thus have likely underestimated the societal benefit of these medications.[28]

This study has several strengths. First, our population-based cohort incorporated data from both the provincial medical prescriptions database, covering all dispensed medications, and centralized laboratory testing for HCV RNA to assess HCV treatment response. This is important as the former ensures that our HCV-infected study population is representative of those being treated in the province, removing the possibility of selection bias, while the latter means that we are comparing SVR and non-SVR patients, rather than treated and untreated patients, which may otherwise introduce cofounding by indication. Second, our study follow-up was sufficiently large to provide power to estimate precise measures of associations for clinically rare outcomes, such as CKD or ESRD and ischemic or hemorrhagic stroke. Third, we only included treatment initiators and censored person-time of follow-up if an SVR patient was re-infected or if a patient who initially failed treatment was re-treated. This allowed us to estimate more accurate measures of associations with treatment-induced clearance that may not have been biased by misclassified exposure or incorrect assignment of person-time at risk.

The results from this study should be interpreted cautiously in light of several limitations. Given that we largely relied on administrative data to assess study covariates and EHM outcomes, it is possible we may have misclassified some exposures or underestimated the incidence of particular EHMs. For example, patients with substance use disorders without a record of contact with the healthcare system may not be correctly classified; however, this misclassification is likely non-differential with respect to treatment response and would bias the results towards the null. Similarly, mood and anxiety disorders and arthritis may not be formally diagnosed and thus our algorithm may only capture more severe cases requiring clinical care. Unmeasured confounding, such as smoking and family history, as well as diet and lifestyle factors may be differentially distributed between SVR and non-SVR groups, in addition to being associated with several EHMs, which may explain some of our observed associations. However, given the large protective effect observed for EHMs, such as T2DM, and CKD or ESRD, one or more potential unmeasured confounders would need to be both strongly skewed and associated with the outcome to account for all of the observed effect, which is improbable. We used SVR from first treatment in primary analysis, which may affect the generalizability of findings, however, we performed additional analysis with SVR from last available treatment, including previous treatment failures, and the results were similar. Although DAAs are the standard of care for HCV treatment, the BC-HTC and other cohorts have not yet accrued enough follow-up time to assess the impact of DAAs on EHMs since they were introduced in 2013. It remains to be seen if viral eradication from interferon-based therapies, compared to all-oral DAAs, has a different effect on the incidence of long-term clinical outcomes, independent from the fact that patients with pre-existing comorbid conditions are now eligible to receive treatment. Finally, given the low incidence rates of most of our EHMs, stratified analyses were largely underpowered to detect small to medium-sized differences in adjusted HRs between subgroups defined by age group, gender, injection drug use, genotype and cirrhosis status.

In conclusion, achieving SVR through interferon-based therapies was associated with a marked reduction in the incidence of several clinically important EHMs, including T2DM, CKD or ESRD, mood and anxiety disorders, and ischemic and hemorrhagic stroke. These findings suggest that expanded access to HCV treatments may reduce the growing burden and healthcare resource utilization associated with chronic extrahepatic disease observed in this population. Additional studies will be needed to assess the broader impact of DAAs on EHMs when longer follow-up becomes available.

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## Conflict of interest

MK has received grant funding via his institution from Roche Molecular Systems, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics and Hologic Inc.

Please refer to the accompanying ICMJE disclosure forms for further details.

## Authors' contributions

NJ, SW, AY, MA, MK participated in the data acquisition. CR and NJ conceived the analysis presented in this paper. CR and NJ designed the study. CR, SW and DJ performed analyses guided by NJ. CR wrote the first draft of the paper. NJ and DJ incorporated revisions. All authors contributed in the interpretation of results, manuscript preparation and revisions. All authors read and approved the final manuscript.

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## Disclaimer

All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

## Supplementary data

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