BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035996
Article Type:	Original research
Date Submitted by the Author:	26-Nov-2019
Complete List of Authors:	Büsch, Katharina; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine Hansson, Fredrik; Devicia AB Holton, Michelle; Lorimer Enterprises Inc Lagging, Martin ; Goteborgs Universitet, Westin, Johan; Goteborgs Universitet Kövamees, Jan; AbbVie Inc, Medical Affairs Sällberg, Matti; Karolinska Institutet, Department of Laboratory Medicine Söderholm, Jonas; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine
Keywords:	HEALTH ECONOMICS, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Gastroenterology < INTERNAL MEDICINE, PUBLIC HEALTH

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Sick leave and disability pension before and after chronic hepatitis C diagnosis and comparison to matched general population comparators

Katharina Büsch[1,2], Fredrik Hansson[3], Michelle Holton[4], Martin Lagging[5], Johan Westin[5], Jan Kövamees[1], Matti Sällberg[2], and Jonas Söderholm[1,2,*]

[1]AbbVie AB, Stockholm, Sweden

[2]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden

[3]Devicia AB, Stockholm, Sweden

[4]Lorimer Enterprises Inc., Red Deer, Canada

[5]Department of Infectious Medicine, Institute of Biomedicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Emails: Katharina Büsch, katharina.buesch@abbvie.com; Fredrik Hansson, fredrik.hansson@clinicaltrialconsultants.se; Michelle Holton, michelle.holton@shaw.ca; Martin Lagging, martin.lagging@medfak.gu.se; Johan Westin, johan.westin@infect.gu.se; Jan Kövamees, jan.kovamees@abbvie.com; Matti Sällberg, Matti.Sallberg@ki.se; Jonas Söderholm, jonas.soderholm@abbvie.com

*Correspondence

Jonas Söderholm

Hemvärnsgatan 9

Box 1523, 171 29 Solna, Sweden

Email: jonas.soderholm@abbvie.com; jonas.soderholm@ki.se; Jonas.soderholm@gmail.com

Running title (40 characters without spaces): Sick leave/disability pension in HCV patients

Keywords: Hepatitis C, chronic; Disability Leave; Sick Leave; Sweden

Word Counts, Tables & Figures

Full article: 3,567 words

Abstract: 288 words

Tables: 2

Figures: 4

Supplemental Tables: 3

Supplemental Figures: 1

Abstract

OBJECTIVE: The objective of this study was to evaluate sick leave and disability pension in patients with chronic hepatitis C virus (HCV) infection patients as compared with matched general population comparators.

DESIGN: Retrospective register study

SETTING: Nationwide

PARTICIPANTS: The register-based study used the Swedish National Patient Register to identify both working-age patients with HCV in 2012 (n=32,021) as well as HCV patients diagnosed between 1999 and 2007 (n=19,362). Sick leave and disability pension data were retrieved from Statistics Sweden (1994–2012), with up to 5 matched individuals from the general population.

PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome was workdays lost due to sick leave episodes (>14 days) and disability pension overall. The secondary outcome was workdays lost per subgroup of patients with chronic HCV.

RESULTS: In 2012, 14% of the HCV patients had ≥1 registered sick leave episode compared with 10% in the matched comparator cohort. For disability pension benefits, results were 30% vs. 8%, respectively. Overall in 2012, 57% of patients with HCV did not have any registered workdays lost, whereas 30% were absent ≥360 days compared with 83% and 9% in the matched cohort, respectively. The mean total number of annual workdays lost in 2012 was 126 days in the HCV patient cohort compared with 40 days in the matched general population comparator cohort. Annual days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis.

CONCLUSIONS: These results show that Swedish HCV patients use more sick days and have a higher frequency of disability pension compared with a comparator cohort from the general Swedish population. Whether earlier diagnosis of and treatment for HCV infection might impact work absence in Sweden warrants further investigation.

ARTICLE SUMMARY: Strengths and limitations of the study

- Previous studies of have focused on describing the sick-leave in a small segment of patients with chronic hepatitis C, this is the first study investigating sick-leave and disability pension on a nation-wide level.

- Hepatitis C is a slowly progressive disease where the patients experience an increasing number of unspecific symptoms until the patient is diagnosed, but only patients diagnosed with chronic HCV are included in the study.
- The actual number of workdays lost are underestimated since only sick leave episodes ≥14 days are included in the data.

Background

Hepatitis C is an infectious viral disease affecting the liver, with Western European prevalence rates estimated to between 0.35 and 1.42%.[1] In Sweden, the prevalence of chronic hepatitis C infection was estimated to be 0.36% in 2013.[2]

Patients with hepatitis C virus (HCV) infection have been shown to have increased work disabilities.[3] Furthermore, models have shown a relationship has been shown between HCV; loss of productivity, increased absenteeism, and higher healthcare benefit costs, which results in substantial economic burden to society.[4–6] A retrospective database analysis showed employees in the United States with HCV infection to have a higher number of lost work days than employees without HCV infection. In addition, they also utilised more sick leave, with an increased use of short-term and long-term disability.[5] The annual cost due to productivity loss in untreated patients with genotype 1 HCV infection in the United States has been estimated to 7.1 billion USD.[6] Before the introduction of the new interferon-free HCV treatment options was the HCV-associated productivity losses in the United Kingdom estimated to rise from 184–367 million GBP in 2010 to 210–427 million GBP in 2035.[7]

The objective of the present study was to evaluate sick leave and disability pension in patients with chronic HCV compared with matched general population comparators using the Swedish National Patient Register. A secondary objective was to examine sick leave and disability pension within certain subgroups (e.g., patients with decompensated cirrhosis, cirrhosis, hepatocellular carcinoma, or liver transplantation) or prevalent patients, as well as sick leave in relation to diagnosis.

Methods

Setting

The population in Sweden was 9.6 million people in 2012 (Statistics Sweden; www.scb.se). Sweden has a universal tax-funded health care system where the Swedish Social Insurance Agency captures information on full or partial sick leave and disability compensations. In 2012 the common retirement age in Sweden was 65 years with people having the right to retire at 61 years of age or choose to continue working until 67 years of age.

Information on Swedish citizens are collected in the nationwide registers using the Swedish unique personal identity number.[8] In the present study the following registries were used; the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labor Market studies (LISA). NPR: Contains all inpatient (1987–2013) and non-primary outpatient care (2001–2013) visits, but no primary care visits.[9] It includes information on both main and contributory diagnoses based on the *International Classification of Diseases* (ICD-9, 1987–1996; ICD-10, 1997-2013). The Cancer Registry covers medical data such as the site of tumor, histologic type, basis, and date of diagnosis (1958–2013). It is mandatory to report all newly detected cancers are mandatory to the registry. However, some cases are only reported to the CDR (i.e., cases denoted as death certificate only and death certificate notification) and are not necessarily included in the Cancer Registry. The PDR includes all prescribed drug use in ambulatory care (2005–2013), although in-hospital use is captured to a lesser extent.[10] It captures information on dates, drugs, and costs for all pharmacy dispensed prescriptions in Sweden using Anatomical Therapeutic Chemical codes. The CDR contains the cause of death with information of year and month of death. The TPR provided information on place of residence, age, sex, country of origin, and emigration status. LISA includes data on sick leave and disability pension for all residents in Sweden ≥16 years of age with information on work-related and socioeconomic variables (e.g. education level, marital status, and days per year of sick leave and disability pension [annual data retrieved for 1994–2012]).

HCV as a diagnosis was introduced with the ICD-10 in 1997 and at the time of data collection was the data on sick leave and disability pension until 2012; thus, the current analysis is based on data from 1997 to 2012.

Informed consent is not required for large-scale registry-based studies in Sweden.[11] Data from the Swedish registries are available for research after ethical and registry approval. The study was approved (Dnr 2014/746-31) by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

Patient and Public Involvement

No patient involved.

Identification of patients with HCV and matched general population comparators

Patients were identified in the NPR using health care visits listing chronic HCV diagnosis (ICD10: B18.2).[12] Only patients of working age (i.e., between 19 and 65 years) were included. Subgroup analyses by age (19–29, 30–39, 40–49, 50–59, 60–65), gender (male/female), education (<9 years, 10–12 years, ≥12 years), disease status (e.g., decompensation cirrhosis [DCC], liver cancer [hepatocellular carcinoma {HCC}], liver transplantation; Table S1 and S2), treatment status (HCV treatment or opioid substitution therapy [OST]; Table S3), and co-infection (HIV or hepatitis B virus; Table S4), were performed. Up to 5 general population controls were matched by age, sex, and county of residence to each patient with HCV at the time of diagnosis.

Definition of outcomes

The outcome was the annual the number of days of sick leave and disability pension (maximum of 365 per year).

Sick leave: As of 1998 the first day of sick leave is not compensated ("waiting period") in Sweden, with day 2 to 14 being paid by employers. Thus, only sick leave episodes >14 days were recorded in the LISA database, as those were paid by the Social Insurance Agency. Any episode occurring within 5 days of a previous episode does not require a new "waiting period" or "sick pay period", thus multiple short-term episodes could waive these periods. I.e. individuals with 0 days registered may in fact have had sick leave episodes ≤14 days, hence that group was denoted "0" registered days to acknowledge this uncertainty.

Disability pension: Disability pension refers to either disability pension (1990–2002) or sickness/activity compensation (2003–2012). In Sweden, disability pension can be either part-time (25%, 50%, 67%, or 75%) or full-time (100%) due to the medical condition. As of 2003 was the disability pension replaced by two types of compensation depending on

age. "Activity compensation" was introduced for younger individuals (19 to 29 years old) whereas older individuals were eligible for "sickness compensation". Both sickness and activity compensation were either time-limited or permanent, but required at least ≥25% reduction in work capacity that was expected for at least 1 year.

Follow-up of patients with HCV and matched general population comparators

Patients with HCV were followed from the date of first visit with an HCV diagnosis during the observation time (index date) until emigration, death, retirement (age 65 years), or study end (December 31, 2012), whichever occurred first. The matched comparators were followed from index date until emigration, death, retirement, until HCV diagnosis, or December 31, 2012, whichever occurred first.

In the analyses of work loss in relation to HCV diagnosis were the patients with HCV followed from 5 years before to 5 years after the year of diagnosis. Patients were included if diagnosed between 1999 and 2007 to allow a ±5-year follow-up time. In addition, patients had to be between 24 and 59 years of age at the time of diagnoses in order to be eligible for benefits during the full follow-up. All codes used are available in the supplemental tables S1 – S4.

Statistics

The annual days of sick leave and disability pension were grouped by categories ("0," 1–90, 91–180, 181–359, and ≥360 days) and presented using arithmetic means.[13] The study calculated the total annual number of days of sick leave and disability pension in 2012 for both cohorts. The difference in workdays lost between the groups was also evaluated using multivariable regression models. The analyses were adjusted for age, sex, and educational level, as well as occurrence of psychiatric diseases and/or liver-related outcomes (defined as history of cirrhosis, F, and/or liver transplantation).

The longitudinal analysis followed the HCV patients and their comparators from 5 years ahead of index date until 5 years after the index date. The impact of interferon-based treatment was analyzed for patients with HCV treated with interferon 2 years before until 2 years after first treatment during 2005 and 2010.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. All p values are two-sided.

Results

Overall, 32,021 patients aged 19 to 64 years were diagnosed with HCV and were living in Sweden in 2012 (HCV prevalent cohort; Table 1).

Table 1 Characteristics of register-identified patients with prevalent CHC aged 19 to 64 years on December 31, 2012, in Sweden and their matched general population comparators

	Patients with CHC in 2012; 19–64 years (n=32,021*)	Matched GenPop comparators in 2012 (n=149,688)
Men, n (%)	20,654 (65%)	95,546 (64%)
Mean (SD) age, y		
At identification/diagnosis	39 (11)	-
In 2012	47 (11)	47 (11)
Highest attained education, n (%)		
<9 years	11,509 (36%)	21,600 (14%)
10–12 years	16,021 (50%)	72,946 (49%)
≥12 years	4159 (13%)	53,866 (36%)
Missing	332 (1%)	1276 (1%)
Marital status at the time of identification, n (%)		

Unmarried	19,725 (62%)	75,011 (50%)
Married	6074 (19%)	57,376 (38%)
Divorced	6111 (19%)	16,539 (11%)
Widow	0	5 (<0.1%)
Missing	111 (0.3%)	757 (1%)
Co-infection, n (%)		
HIV	672 (2%)	210 (0.1%)
HBV	3222 (10%)	377 (0.3%)
Registered CHC-related outcome, n (%)†		
Liver cirrhosis	2346 (7%)	213 (0.1%)
Decompensated cirrhosis	1041 (3%)	31 (0%)
Hepatocellular carcinoma	408 (1%)	125 (0.1%)
Liver transplantation	289 (1%)	48 (<0.1%)
HCV treatment since 2005	6234 (19%)	-
OST treatment since 2005	3735 (12%)	1102 (1%)

CHC=chronic hepatitis C; HBV=hepatitis B virus; HCV=hepatitis C virus; LISA=Longitudinal Integrated Database for Health Insurance and Labor Market Studies; NPR=National Patient Register; OST=opioid substitution therapy; SD=standard deviation.

*169 patients with CHC were excluded, as there was no data available in the LISA dataset.

†Interpretation of data should be done with caution, as certain outcomes such as liver cirrhosis were likely underreported in the NPR; all codes used to define outcomes are provided in Table S1, S2, S3, and S4.

Prevalence and days of sick leave and disability pension in 2012

Fourteen percent of patients with HCV had ≥1 registered sick leave episode(s) in 2012 compared with 10% in the matched general population comparator cohort. Eight percent of individuals in the matched general population received disability pension benefits, compared with 30% of patients with HCV. In total, 43% of patients with HCV and 17% of individuals in the matched general population comparator cohort had at least one registered sick leave episode or received disability pension benefits in 2012 (Table 2).

Table 2 Annual number of days of sick leave and disability pension in 2012 in patients with register-identified CHC and matched general population comparators

	Patients with CHC in 2012; 19–64 years (n=32,021*)	**Matched GenPop comparators in 2012 (n=149,688)**	**Difference (days)**
Mean (SD) total annual number of days during follow-up	**106 (155)**	**34 (97)**	**72**
Sick leave	27 (78)	13 (55)	14
Disability pension, gross	80 (148)	21 (84)	59
Disability pension, net	76 (143)	18 (75)	58
Mean (SD) total days in 2012	**126 (166)**	**40 (107)**	**86**
Sick leave	22 (72)	11 (88)	11
Disability pension, gross	106 (164)	29 (98)	77
Disability pension, net	101 (159)	25 (88)	76

CHC=chronic hepatitis C; SD=standard deviation.

NOTE. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period (waived only under certain circumstances).

*Matched general population comparators were matched on age, sex, education, and place of residency at the time of diagnosis.

The prevalence of receiving a disability pension was similar among men and women, but was higher among older individuals, those with co-infection (HCV and HIV or hepatitis B virus), and those receiving OST (Figure S1). It was lower among those with a higher educational level and those who previously had been treated for HCV infection. The prevalence of sick leave was higher among women and those with higher education; there were minor variations by age. Prevalence of sick leave or disability pension use was always higher among patients with an HCV–related complication such as cirrhosis, DCC, HCC, or liver transplantation.

Overall, fewer patients with HCV (57%) did not have any registered workdays lost in 2012 in relation to the 83% without any registered workdays lost in matched general population comparator cohort. A greater proportion (30%) of patients with HCV were absent ≥360 days than in the matched general population comparator cohort (9%, p<0.001; Figure 1). The median number of workdays lost was "0" in both cohorts, thus the distribution of workdays lost in 2012 was non-normal.

Among prevalent patients, the annual number of workdays lost was generally higher among older patients, patients with lower education, patients with co-infection, and among patients with liver complications such as DCC, HCC, and liver transplantation (Figure 2). The average total annual number of workdays lost in 2012 was 126 in the HCV patient cohort and 40 in the matched general population comparator cohort (Table 2). When only those with a registered episode were analysed, the mean total annual number of workdays lost rose to 296 days among patients with HCV, a trend that was observed among all subgroups (Figure 2).

The multivariable regression model was adjusted for age, sex, and educational level, showed patients with HCV to have on average 75 more workdays lost compared with the general population. The number of workdays lost decreased to 60 days when considering psychiatric diseases. When also adjusting for any history of either cirrhosis, HCC, or liver transplantation the estimate was reduced to 55 days. The independent factors associated with a greater number of workdays lost were older age, lower level of education, female sex, psychiatric diseases, and history of liver-related outcomes were all independently and significantly (p<0.001).

Longitudinal work loss in relation to diagnosis

Among all patients with HCV, 19,362 patients were diagnosed between 1999 and 2007 and qualified for a follow-up of work loss for up to 5 years before and after diagnosis. Five years before diagnosis, 37% of patients with HCV had workdays lost registered, which increased to 51% in the year of diagnosis and remained constant thereafter. The workdays lost for the matched general population comparators for these 19,362 patients remained between 16% and 21% throughout the longitudinal analysis (Figure 3). More than 30% of patients with HCV were almost fully work disabled already 1 year after diagnosis compared with approximately 10% in the matched general population comparators. Thus, patients with HCV were 3 times as likely to be fully work disabled compared with the matched general population cohort.

The mean annual workdays lost increased from 86 days to 146 days from 5 years before HCV diagnosis to 1 year after diagnosis. The number of workdays lost were always considerably higher among patients with HCV (5 years before HCV diagnosis: 86 vs. 28 days = difference of 59 days; at the year of HCV diagnosis: 136 vs. 43 days = difference of 92 days; 5 years after HCV diagnosis: 148 vs. 50 days = difference of 97 days; Figure 3).

Among the 5,177 patients treated with interferon-based treatments between 2005 and 2010, the mean annual number of sick leave days was approximately 30 days before the start of treatment. Sick leave days increased to 60 days during the year of treatment initiation and decreased to pre-treatment levels (approximately 30 days) 2 years after treatment initiation (Figure S2). In relation to interferon-based treatment, no large differences were observed in mean annual disability pension days. The trend that showed an increase in mean disability pension days before treatment initiation was no longer evident after treatment.

Discussion

Hepatitis C virus infection is a slowly developing disease, often beginning with vague symptoms such as fatigue, loss of appetite, and headache. These symptoms often begin to manifest well before the patient is diagnosed with HCV, and these comorbidities are believed to affect the general well-being of patients, with an accompanying increased need for sick leave and disability pension. However, the use of sick leave/disability has only been investigated in a few studies, with the largest examining data from 1,664 patients with an HCV diagnosis who were employed in the United States. In order to get the full picture of the sick leave and disability pension for patients with HCV in a whole country and to avoid the bias of only analysing employed patients with HCV, the study set out to investigating the sick leave and disability pension for all diagnosed patients with HCV of working age in Sweden. The diagnosis rate of HCV differs between regions, with an estimated 75% of the cases of HCV in the United States remaining undiagnosed.[14] In contrast, globally the diagnosis rate in Sweden is fairly high, with an estimated 20% of patients remaining undiagnosed.[15] This, in combination with the virtually complete national coverage of the Swedish registers, makes Sweden a country well-suited for the investigation of the burden of HCV on the welfare system.

Most importantly did the study show that 42% of the patients with HCV received compensation from the Social Insurance Agency in form of sick leave or received a disability pension in 2012 compared with 17% of the comparators. In total, the patients with HCV lost an average of 87 extra workdays per year compared with matched comparators. The difference in the number of sick leave days, as well as disability pension, could be explained by the inherent differences between patients with and without HCV infection, with riskier lifestyle and psychiatric disorders being more common in patients in the HCV cohort.[16,17] This could explain the greater frequency of disability pension and higher mean sick leave days noted 5 years before HCV diagnosis, where the annual number of days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis; in the comparator cohort, there was only an increase of 15 days during this time (Figure 3). However, despite starting from a higher rate, there was a rapid increase in both mean sick leave and disability pension in the years leading up to HCV diagnosis, whereas no such rapid increase was seen in the match comparators. This suggests that patients most likely experience increased symptoms as the disease progress that leads to a greater utilisation of sick leave and likely more visits to both primary care physicians and specialists until diagnosis. In addition, after adjusting for psychiatric disease, the difference in sick leave between the 2 groups remained; this suggests that HCV impacts the general health status of patients. It is tempting

to hypothesize that earlier diagnosis and treatment of patients with HCV would slow down the increasing need for sick leave and disability pension; however, the present study was not designed to investigate this. Nevertheless, other studies have suggested that earlier treatment benefits both society and the individual patient.[18–20]

In line with previous studies, there was an increase in mean sick leave days noted during the first year of treatment, which is likely due to the side effects associated with interferon-based treatment.[21,22] The newly introduced interferon-free regimens for patients with HCV infection have a more favourable safety profile compared with interferon-based regimens.[23] This would most likely reduce the number of sick leave days needed during treatment. The difference between interferon-based and interferon-free regimens will need to be analysed further when data from interferon-free treatments become available in the registers.

Registry studies on sick leave and disability pension contains the actual number of days the social insurance is used per person, compared with self-reported information that is more prone to bias. However, the data is only as valid as the information entered, but the nationwide Swedish registers are considered to be >99% complete. Nationwide large-scale registries allow assessment of subgroup variations and the use of up to 5 matched comparators from the general population instead of retrospective matching strengthen the results of the study.

One main limitation of the study is that the patients with HCV were identified in the NPR that is dependent on physician entered diagnoses from inpatient and non-primary outpatient care (previously discussed for this cohort[24]), and any mistake when entering a diagnosis could for example consider individuals without HCV to be patients with HCV. Importantly, the first visit may not necessary be the first HCV diagnosis given that the specific ICD code for HCV (B18.2 ICD-10) has only been available since 1997, thus the time of diagnosis must be interpreted with caution. As mentioned in the methods, the Social Insurance Agency data only includes sick leave episodes >14 days, as these the first episodes are covered by the employer. This will result in an underestimation of the actual number of workdays lost; however, this applies to both cohorts. Interestingly, the main difference in work absence for US employees with HCV was driven by the short-term disability (defined as sick leave between 14 days and 6 months[5,25]), thus suggesting the present study would capture the HCV-mediated impact on sick leave

Conclusions

To our knowledge, this is the largest study on sick leave and disability pension in patients with HCV to date and the first longitudinal study that investigated this in relation to time of diagnosis. These results indicate that patients with HCV use more sick days and that they have a higher frequency of disability pension compared with a comparator cohort from the general population. However, any impact of earlier hepatitis C diagnosis and if virologic cure reduces work absence is not answered by this study and needs to be further investigated. Finally, the results may be less generalizable to countries where private health insurance is more common.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden. Informed consent is not needed for large registry-based studies in Sweden.[11]

CONSENT FOR PUBLICATION: Not applicable, only aggregated data included in the study. Informed consent is not needed for large registry-based studies in Sweden.[11]

AVAILABILITY OF DATA AND MATERIALS: The datasets generated and/or analysed during the current study where retrieved from the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labor Market studies (LISA) are available for research after ethical approval. The ethical approval for the present study does not allow for sharing data to persons not in the ethical approval.

COMPETING INTERESTS: M. Lagging has consultancies with AbbVie, Gilead, and MSD/Merck and is a member of the speakers' bureau for AbbVie, Gilead, and MSD/Merck. M. Sällberg is founder and owner of Svenska Vaccinfabriken AB. F. Hansson reports no conflicts of interest. M. Holton is President of Lorimer Enterprises Inc., a company that has consulted for AbbVie. J. Westin has had paid teaching assignments for AbbVie, Gilead, and MSD/Merck. J. Söderholm and J. Kövamees are employees of AbbVie and may hold AbbVie stocks or stock options. K. Büsch was an employee of AbbVie at the time of the study and may hold AbbVie stocks or stock options.

FUNDING: The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data/input analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication.

AUTHOR CONTRIBUTIONS: The concept of the study was designed by KB, JK, and JS. FH and KB managed the database. KB, FH, MH, and JS interpreted the data with support from ML, JK, and JW. KB and JS were the major contributors in writing the manuscript. All authors critically revised the manuscript and approved the final version that was submitted.

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Figure legends

Figure 1

Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified HCV population (n=32,021) and matched general population comparators (n=149,688).

HCV=chronic hepatitis C. "0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

Mean total annual number of days of work loss in 2012 in the Swedish register–identified HCV population (n=32,021); among all patients and those with registered sick leave or disability pension.

HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension days. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 3

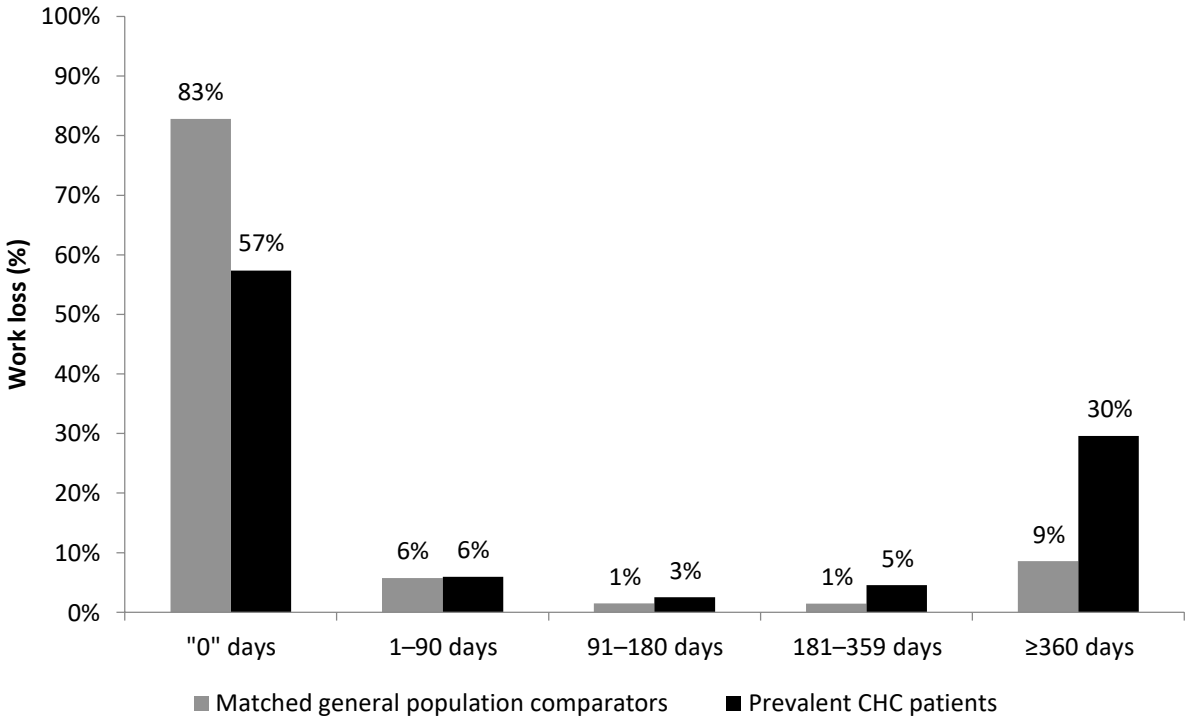
Annual days of sick leave and disability pension 5 years before to 5 years after HCV diagnosis.

Patients with register-identified HCV who were diagnosed between the age of 24 and 59 years (n=19,362) and matched general population comparators (n= 92,697) in a longitudinal analysis of annual days of sick leave and disability pension from 5 years before to 5 years after diagnosis during 1999–2007.

HCV=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population

comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date). The figures show the full distribution of days in categories and annual mean number of total days.

Figure 1 Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified CHC population (n=32,021) and matched general population comparators (n=149,688).



CHC=chronic hepatitis C.

"0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

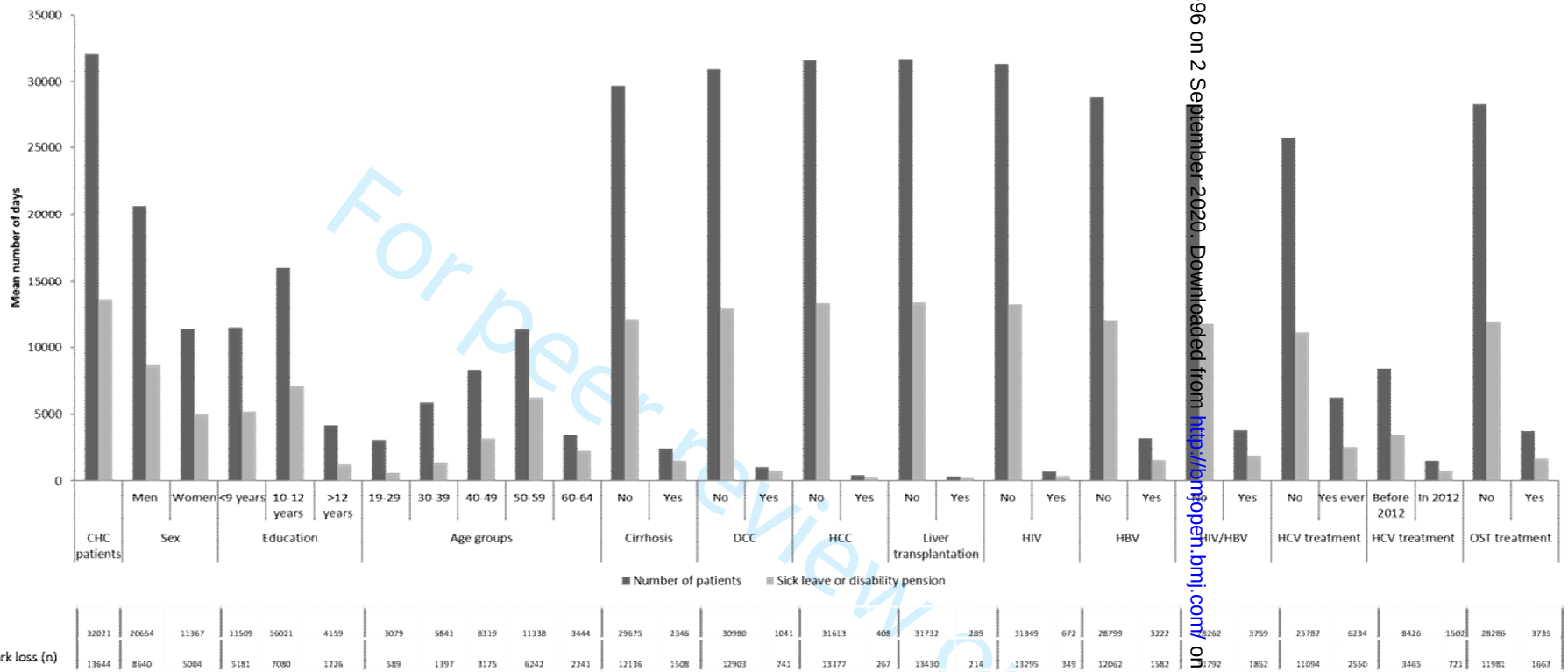


Figure 3

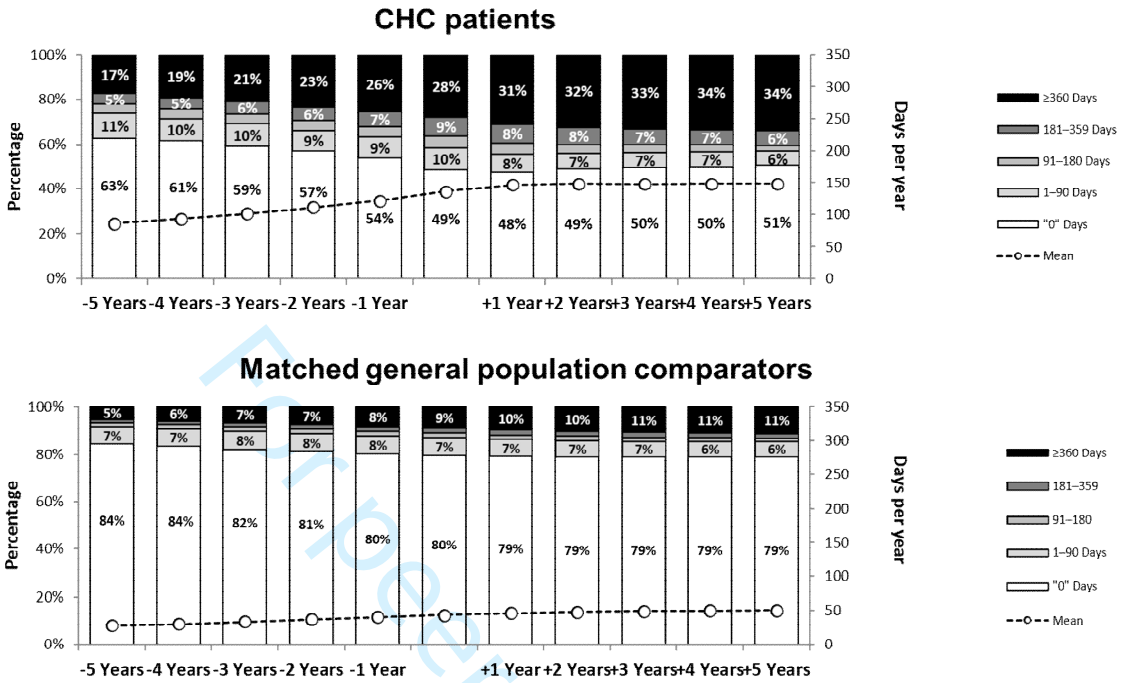
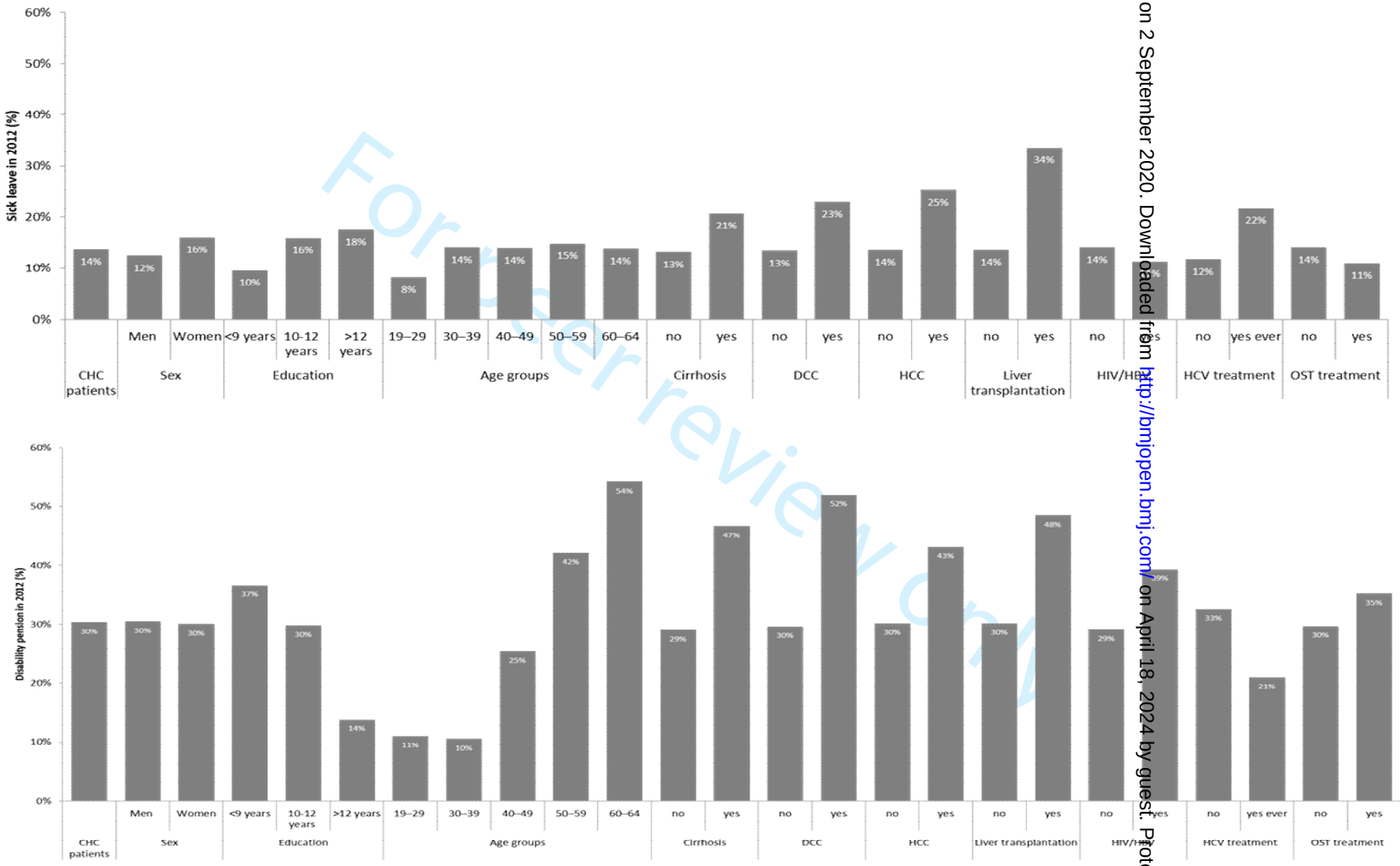
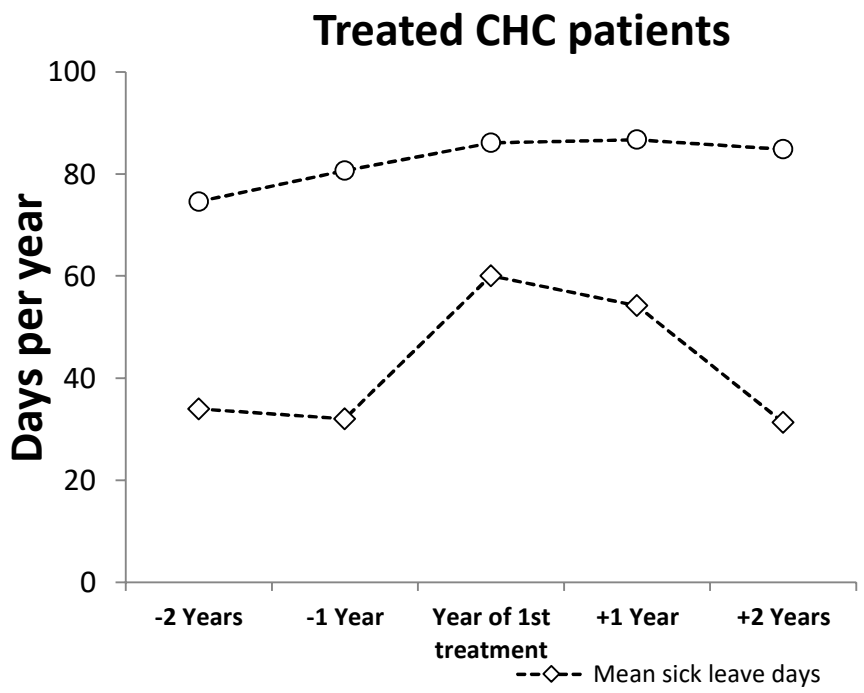


Figure S1 - Proportion of patients on any disability pension or sick leave in 2012 in the Swedish register–identified HCV population (n=32,021).



HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension. Some sick leave episodes ≤14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Figure S2 Mean annual days of sick leave and disability pension in patients with register-identified CHC in a longitudinal analysis from 2 years before to 2 years after first treatment initiation.



CHC=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Supplementary Tables

Table S1 ICD codes used for hepatitis C and liver-related complications

Diseases	ICD9 (1987-1996)	ICD10 (1997-2013)
Hepatitis		
Unspecific/virus hepatitis	070E, 070F, 070G, 070X	B19
Acute hepatitis C	-	B17.1
Chronic hepatitis C	-	B18.2
Chronic active HCV with cirrhosis		*B18.2E*
Chronic HCV with fibrosis		*B18.2F*
Chronic HCV with cirrhosis		*B18.2G*
Liver-related complications / liver disease		
Liver complications*	570, 571A-571G, 571X, 571W, 572C-572E, 572W, 573W	K70, K72, K73, K74, K76
Complication of liver disease	452, 456A-456C	I81, I85, I98.2, I98.3
Symptoms	782E, 789B-789C, 789F	R16, R17, R18,
Hepatocellular carcinoma (HCC)**	155A, 155C, 235D, 239A	C22.0, C22.9, D37.6
Liver transplantation***	V42H	Z94.4

* Plus sub-codes to B18.2E-G (see above); ** Plus ICD7 codes 155.0 in the cancer register; *** Plus surgery codes (see Table S4)

Liver-related complications included liver complications defined fibrosis, cirrhosis, liver failure, complications of the liver defined as portal vein thrombosis, esofageal varices and symptoms including ascites, jaundice.

Table S2 Surgical procedure codes used in the analysis

Surgical procedure	National classification of procedures (till 1996)	NOMESCO classification of surgical procedures (since 1997)
Liver transplantation	5200	JJC

Table S3 ATC codes used in the analysis

Prescribed drugs	**ATC codes (2005-2013)**
Peg-Interferon and ribavirin	J05AB04, L03AB10, L03AB11, L03AB60, L03AB61
Protease inhibitors	J05AE11, J05AE12

Table S4 ICD codes used for co-infections and psychiatric disorders

Diseases	**ICD9 (1987-1996)**	**ICD10 (1997-2013)**
Co-infections		
HIV	279K, 279L	B20-B24
Hepatitis B	070C, 070D	B18.0, B18.1
Other comorbidities		
Psychiatric disorders	F00-F99	290-319

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8

	(e) Describe any sensitivity analyses	Done in ref 2

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035996.R1
Article Type:	Original research
Date Submitted by the Author:	20-May-2020
Complete List of Authors:	Büsch, Katharina; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine Hansson, Fredrik; Devicia AB Holton, Michelle; Lorimer Enterprises Inc Lagging, Martin ; Goteborgs Universitet, Westin, Johan; Goteborgs Universitet Kövamees, Jan; AbbVie Inc, Medical Affairs Sällberg, Matti; Karolinska Institutet, Department of Laboratory Medicine Söderholm, Jonas; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Gastroenterology and hepatology, Infectious diseases, Public health
Keywords:	HEALTH ECONOMICS, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Gastroenterology < INTERNAL MEDICINE, PUBLIC HEALTH

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Sick leave and disability pension in patients with chronic hepatitis C compared to a matched general population: A nationwide register study

Katharina Büsch[1,2], Fredrik Hansson[3], Michelle Holton[4], Martin Lagging[5], Johan Westin[5], Jan Kövamees[1], Matti Sällberg[2], and Jonas Söderholm[1,2,*]

[1]AbbVie AB, Stockholm, Sweden

[2]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden

[3]Devicia AB, Stockholm, Sweden

[4]Lorimer Enterprises Inc., Red Deer, Canada

[5]Department of Infectious Medicine, Institute of Biomedicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Emails: Katharina Büsch, katharina_buesch@yahoo.de; Fredrik Hansson, fredrik.hansson@ctc-ab.se; Michelle Holton, michelle.holton@shaw.ca; Martin Lagging, martin.lagging@medfak.gu.se; Johan Westin, johan.westin@infect.gu.se; Jan Kövamees, jan.kovamees@abbvie.com; Matti Sällberg, Matti.Sallberg@ki.se; Jonas Söderholm, jonas.soderholm@abbvie.com

*__Correspondence__

Jonas Söderholm

Hemvärnsgatan 9

Box 1523, 171 29 Solna, Sweden

Email: jonas.soderholm@abbvie.com; jonas.soderholm@ki.se; Jonas.soderholm@gmail.com

Running title (40 characters without spaces): Sick leave/disability pension in HCV patients

Keywords: Hepatitis C, chronic; Disability Leave; Sick Leave; Sweden

Word Counts, Tables & Figures

Full article: 3,269 words

Abstract: 284 words

Tables: 2

Figures: 3

Supplemental Tables: 3

Supplemental Figures: 1

Abstract

OBJECTIVE: The objective of this study was to evaluate sick leave and disability pension in patients with chronic hepatitis C virus (HCV) infection as compared with a matched general population cohort.

DESIGN: Retrospective register study

SETTING: Nationwide in Sweden

PARTICIPANTS: This register-based study used the Swedish National Patient Register to identify working-age patients with HCV in 2012 (n=32,021) who were diagnosed between 1999 and 2007 (n=19,362). Sick leave and disability pension data were retrieved from Statistics Sweden (1994–2012), with up to 5 matched individuals from the general population.

PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome was workdays lost due to sick leave episodes (>14 days) and disability pension overall. The secondary outcome was workdays lost per subgroup of patients with chronic HCV.

RESULTS: In 2012, 14% of the HCV patients had ≥1 registered sick leave episode compared with 10% in the matched comparator cohort. For disability pension benefits, results were 30% vs. 8%, respectively. Overall, in 2012, 57% of patients with HCV did not have any registered workdays lost, whereas 30% were absent ≥360 days compared with 83% and 9% in the matched cohort, respectively. The mean total number of annual workdays lost in 2012 was 126 days in the HCV patient cohort compared with 40 days in the matched general population comparator cohort. Annual days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis.

CONCLUSIONS: These results show that Swedish HCV patients used more sick days and have a higher frequency of disability pension compared with a comparator cohort from the general Swedish population. Whether earlier diagnosis of HCV and treatment might impact work absence in Sweden warrants further investigation.

ARTICLE SUMMARY: Strengths and limitations of the study

- Previous studies focused on describing sick leave in a small segment of patients with chronic hepatitis C, whereas this is the first study to investigating sick leave and disability pension on a nationwide level.

- The registers contain routinely collected data, i.e. limiting the risk for sampling bias.
- The diagnosis analysed was retrieved from Swedish patient register and was not validated, however the Swedish patient register has previously shown high reliability.
- The registers do not contain information on treatment outcome, so analysis on the impact of viral eradication and workdays lost was not feasible.
- The actual number of workdays lost are underestimated since only sick leave episodes ≥14 days are registered.

Background

Hepatitis C is an infectious viral disease affecting the liver, with Western European prevalence rates estimated between 0.35 and 1.42%.[1] In Sweden, the prevalence of chronic hepatitis C infection was estimated to be 0.36% in 2013.[2]

Patients with hepatitis C virus (HCV) infection have been shown to have increased work disabilities.[3] Furthermore, models have shown a relationship between HCV and loss of productivity, increased absenteeism, and higher healthcare benefit costs, which results in substantial economic burden to society.[4–6] A retrospective database analysis showed employees in the United States with HCV infection to have a higher number of lost workdays than employees without HCV infection. In addition, they also utilised more sick leave, with an increased use of short-term and long-term disability.[5] The annual cost due to productivity loss in untreated patients with genotype 1 HCV infection in the United States has been estimated to 7.1 billion USD.[6] Before the introduction of the new interferon-free HCV treatment options the HCV-associated productivity losses in the United Kingdom were estimated to rise from 184–367 million GBP in 2010 to 210–427 million GBP in 2035.[7]

The objective of the present study was to evaluate sick leave and disability pension in patients with chronic HCV compared with matched general population comparators using the Swedish National Patient Register. A secondary objective was to examine sick leave and disability pension within certain subgroups (e.g., patients with decompensated cirrhosis, cirrhosis, hepatocellular carcinoma, or liver transplantation) or prevalent patients, as well as sick leave in relation to diagnosis.

Methods

Setting

The population in Sweden was 9.6 million people in 2012 (Statistics Sweden; www.scb.se). Sweden has a universal tax-funded health care system where the Swedish Social Insurance Agency captures information on full or partial sick leave and disability compensations. In 2012 the common retirement age in Sweden was 65 years with people having the right to retire at 61 years of age or choose to continue working until 67 years of age.

Information on Swedish citizens are collected in the nationwide registers using the Swedish unique personal identity number.[8] In the present study the following registries were used; the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labour Market studies (LISA). The NPR contains

all inpatient (1987–2013) and non-primary outpatient care (2001–2013) visits, but it does not capture any primary care visits.[9] The NPR includes information on both main and contributory diagnoses based on the *International Classification of Diseases* (ICD-9, 1987–1996; ICD-10, 1997-2013). The Cancer Registry covers medical data such as the site of tumour, histologic type, basis, and date of diagnosis (1958–2013). It is mandatory to report all newly detected cancers to the registry. However, some cases are only reported to the CDR (i.e., cases denoted as death certificate only and death certificate notification) and are not necessarily included in the Cancer Registry. The PDR includes all prescribed drug use in ambulatory care (2005–2013), although in-hospital drug use is captured to a much lesser extent.[10] It contains information on dates, drugs, and costs for all pharmacy dispensed prescriptions in Sweden using Anatomical Therapeutic Chemical codes. The CDR contains information on the cause of death with information on the year and month of death. The TPR provides information on place of residence, age, sex, country of origin, and emigration status. LISA includes data on sick leave and disability pension for all residents in Sweden ≥16 years of age with information on work-related and socioeconomic variables (e.g. education level, marital status, and days per year of sick leave and disability pension [annual data retrieved for 1994–2012]).

HCV as a diagnosis was introduced with the ICD-10 in 1997 and at the time of data collection (April 2014) was the data on sick leave and disability pension available until December 31, 2012; thus, the current analysis is based on data from 1997 to 2012.

Informed consent is not required for large-scale registry-based studies in Sweden.[11] Data from the Swedish registries are available for research after ethical and registry approval. The study was approved (Dnr 2014/746-31) by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

Patient and Public Involvement

No patient involved.

Identification of patients with HCV and matched general population comparators

Patients were identified in the NPR using health care visits with a chronic HCV diagnosis (ICD10: B18.2),[12] as described previously for this cohort.[2] Only patients of working age (i.e., between 19 and 65 years) were included. Subgroup analyses by age (19–29, 30–39, 40–49, 50–59, 60–65), gender (male/female), education (<9 years, 10–12

years, ≥12 years), disease status (e.g., decompensation cirrhosis [DCC], liver cancer [hepatocellular carcinoma {HCC}], liver transplantation; Table S1 and S2), treatment status (HCV treatment or opioid substitution therapy [OST]; Table S3), and co-infection (HIV or hepatitis B virus; Table S4), were performed. Up to 5 general population controls were matched by age, sex, and county of residence to each patient with HCV at the time of diagnosis.

Definition of outcomes

The outcome was the annual number of days of sick leave and disability pension (maximum of 365 per year).

Sick leave: As of 1998 the first day of sick leave is not compensated ("waiting period") in Sweden, with day 2 to 14 being paid by employers. Thus, only sick leave episodes >14 days were recorded in the LISA database, as those were paid by the Social Insurance Agency. Any episode occurring within 5 days of a previous episode does not require a new "waiting period" or "sick pay period", thus multiple short-term episodes could waive these periods. I.e. individuals with 0 days registered may in fact have had sick leave episodes ≤14 days, hence that group was denoted "0" registered days to acknowledge this uncertainty.

Disability pension: Disability pension refers to either disability pension (1990–2002) or sickness/activity compensation (2003–2012). In Sweden, disability pension can be either part-time (25%, 50%, 67%, or 75%) or full-time (100%) based on the type and severity of the medical condition. As of 2003 was the disability pension replaced by two types of compensation depending on age. "Activity compensation" was introduced for younger individuals (19 to 29 years old) whereas older individuals were eligible for "sickness compensation". Both sickness and activity compensation were either time-limited or permanent but required at least ≥25% reduction in work capacity that was expected for at least 1 year. Gross disability pension refers to the number away from work, whereas net disability pension refers to the net time away, e.g. 50% sick leave for 14 days would equal 14 days gross disability pension and 7 days net disability pension. [13]

Follow-up of patients with HCV and matched general population comparators

Patients with HCV were followed from the date of first visit with an HCV diagnosis during the observation time (index date) until emigration, death, retirement (age 65 years), or study end (December 31, 2012), whichever occurred first. The matched comparators were followed from index date until emigration, death, retirement, until HCV diagnosis, or

December 31, 2012, whichever occurred first. The prevalent cohort included patients alive and living in Sweden as of December 31, 2012.

For the longitudinal analyses of work loss due to sick leave and disability pension the patients with HCV were followed from 5 years before to 5 years after diagnosis. Patients were included if diagnosed between 1999 and 2007 to allow a ±5-year follow-up time. In addition, patients had to be between 24 and 59 years of age at the time of diagnoses in order to be eligible for benefits during the full follow-up. All codes used are available in the supplemental tables S1 – S4.

Statistics

The annual days of sick leave and disability pension were grouped by categories ("0," 1–90, 91–180, 181–359, and ≥360 days) and presented using arithmetic means.[14] The study calculated the total annual number of days of sick leave and disability pension in 2012 for both cohorts. The difference in workdays lost between the groups was also evaluated using multivariable regression models. The analyses were adjusted for age, sex, and educational level, as well as occurrence of psychiatric diseases and/or liver-related outcomes (defined as history of cirrhosis, mental and behavioural disorders, and/or liver transplantation), if the goodness of fit was >0.6.

The longitudinal analysis followed the HCV patients and their comparators from 5 years ahead of index date until 5 years after the index date. The impact of interferon-based treatment was analysed for patients with HCV treated with interferon 2 years before until 2 years after first treatment during 2005 and 2010.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. All p values are two-sided.

Results

Overall, 32,021 patients aged 19 to 64 years were diagnosed with HCV and were living in Sweden on December 31, 2012 (HCV prevalent cohort; Table 1).

Table 1 Characteristics of register-identified patients with prevalent HCV aged 19 to 64 years on December 31, 2012, in Sweden and their matched general population comparators

	Patients with HCV in 2012; 19–64 years (n=32,021*)	Matched GenPop comparators in 2012 (n=149,688)
Men, n (%)	20,654 (65%)	95,546 (64%)
Mean (SD) age, y		
At identification/diagnosis	39 (11)	-
In 2012	47 (11)	47 (11)
Highest attained education, n (%)		
<9 years	11,509 (36%)	21,600 (14%)
10–12 years	16,021 (50%)	72,946 (49%)
≥12 years	4159 (13%)	53,866 (36%)
Missing	332 (1%)	1276 (1%)
Marital status at the time of identification, n (%)		

Unmarried	19,725 (62%)	75,011 (50%)
Married	6074 (19%)	57,376 (38%)
Divorced	6111 (19%)	16,539 (11%)
Widow	0	5 (<0.1%)
Missing	111 (0.3%)	757 (1%)
Co-infection, n (%)		
HIV	672 (2%)	210 (0.1%)
HBV	3222 (10%)	377 (0.3%)
Registered HCV -related outcome, n (%)†		
Liver cirrhosis	2346 (7%)	213 (0.1%)
Decompensated cirrhosis	1041 (3%)	31 (0%)
Hepatocellular carcinoma	408 (1%)	125 (0.1%)
Liver transplantation	289 (1%)	48 (<0.1%)
HCV treatment since 2005	6234 (19%)	-
OST treatment since 2005	3735 (12%)	1102 (1%)

HBV=hepatitis B virus; HCV=hepatitis C virus; LISA=Longitudinal Integrated Database for Health Insurance and Labour Market Studies; NPR=National Patient Register; OST=opioid substitution therapy; SD=standard deviation.

*169 patients with HCV were excluded, as there was no data available in the LISA dataset.

†Interpretation of data should be done with caution, as certain outcomes such as liver cirrhosis were likely underreported in the NPR; all codes used to define outcomes are provided in Table S1, S2, S3, and S4.

Prevalence and days of sick leave and disability pension in 2012

Fourteen percent of patients with HCV had ≥1 registered sick leave episode(s) in 2012 compared with 10% in the matched general population comparator cohort. Eight percent of individuals in the matched general population received disability pension benefits, compared with 30% of patients with HCV. In total, 43% of patients with HCV and 17% of individuals in the matched general population comparator cohort had at least one registered sick leave episode or received disability pension benefits in 2012 (Table 2).

Table 2 Annual number of days of sick leave and disability pension in 2012 in patients with register-identified HCV and matched general population comparators

	Patients with HCV in 2012; 19–64 years (n=32,021*)	**Matched GenPop comparators in 2012 (n=149,688)**	**Difference (days)**
Mean (SD) total annual number of days during follow-up	**106 (155)**	**34 (97)**	**72**
Sick leave	27 (78)	13 (55)	14
Disability pension, gross	80 (148)	21 (84)	59
Disability pension, net	76 (143)	18 (75)	58
Mean (SD) total days in 2012	**126 (166)**	**40 (107)**	**86**
Sick leave	22 (72)	11 (88)	11
Disability pension, gross	106 (164)	29 (98)	77
Disability pension, net	101 (159)	25 (88)	76

HCV =chronic hepatitis C; SD=standard deviation.

NOTE. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period (waived only under certain circumstances).

*Matched general population comparators were matched on age, sex, and place of residency at the time of diagnosis.

The prevalence of receiving a disability pension was similar among men and women, but was higher among older individuals, those with co-infection (HCV and HIV or hepatitis B virus), and those receiving OST (Figure S1). It was lower among those with a higher educational level and those who previously had been treated for HCV infection. The prevalence of sick leave was higher among women and those with higher education, with minor variations by age. Prevalence of sick leave or disability pension use was always higher among patients with an HCV–related complication such as cirrhosis, DCC, HCC, or liver transplantation.

Overall, fewer patients with HCV did not have any registered workdays lost in 2012 compared to the matched general population comparator cohort (57% vs. 83%). A greater proportion (30%) of patients with HCV were absent ≥360 days than in the matched general population comparator cohort (9%, p<0.001; Figure 1). The median number of workdays lost was "0" in both cohorts, thus the distribution of workdays lost in 2012 was non-normal.

Among prevalent patients, the annual number of workdays lost was generally higher among older patients, patients with lower education, patients with co-infection, and among patients with liver complications such as DCC, HCC, and liver transplantation (Figure 2). The average total annual number of workdays lost in 2012 was 126 in the HCV patient cohort and 40 in the matched general population comparator cohort (Table 2). When only those with a registered episode were analysed, the mean total annual number of workdays lost rose to 296 days among patients with HCV, a trend that was observed among all subgroups (Figure 2).

The multivariable regression model was adjusted for age, sex, and educational level, showed patients with HCV to have on average 75 more workdays lost compared with the general population. The number of workdays lost decreased to 60 days when considering psychiatric diseases. When also adjusting for any history of either cirrhosis, HCC, or liver transplantation the estimate was reduced to 55 days. The independent factors associated with a greater number of workdays lost were older age, lower level of education, female sex, psychiatric diseases, and history of liver-related outcomes were all independently and significantly (p<0.001).

Longitudinal work loss in relation to diagnosis

Among all patients with HCV 19,362 patients were diagnosed between 1999 and 2007, thus qualified for the longitudinal analysis that followed work loss for up to 5 years before and after diagnosis. Five years before diagnosis,

37% of patients with HCV had workdays lost registered, which increased to 51% in the year of diagnosis and thereafter remained constant. The workdays lost for the matched general population comparators for these 19,362 patients remained between 16% and 21% throughout the longitudinal analysis (Figure 3). More than 30% of patients with HCV were almost fully work disabled already 1 year after diagnosis compared with approximately 10% in the matched general population comparators. Thus, patients with HCV were 3 times as likely to be fully work disabled compared with the matched general population cohort.

The mean annual workdays lost increased from 86 days to 146 days from 5 years before HCV diagnosis to 1 year after diagnosis. The number of workdays lost were always considerably higher among patients with HCV (5 years before HCV diagnosis: 86 vs. 28 days = difference of 59 days; at the year of HCV diagnosis: 136 vs. 43 days = difference of 92 days; 5 years after HCV diagnosis: 148 vs. 50 days = difference of 97 days; Figure 3).

Among the 5,177 patients treated with interferon-based treatments between 2005 and 2010, the mean annual number of sick leave days was approximately 30 days before the start of treatment. Sick leave days increased to 60 days during the year of treatment initiation followed be a decrease to pre-treatment levels (approximately 30 days) 2 years after treatment initiation (Figure S2). No large differences were observed in mean annual disability pension days in relation to interferon-based treatment. The trend that showed an increase in mean disability pension days before treatment initiation was no longer evident after treatment.

Discussion

Hepatitis C infection is a slowly developing disease that often begins with vague symptoms such as fatigue, loss of appetite, and headache. These symptoms often begin to manifest well before the patient is diagnosed with HCV. The comorbidities are believed to affect the general well-being of the patients with an accompanying increased need for sick leave and disability pension. However, the use of sick leave/disability has only been investigated in a few studies, with the largest examining data from 1,664 patients with HCV diagnoses who were employed in the United States. In order to get the full picture of the sick leave and disability pension use for patients with HCV in an entire country and to avoid the bias of only analysing employed patients with HCV, the present study set out to investigating the sick leave and disability pension for all diagnosed patients with HCV of working age in Sweden. The diagnosis rate of HCV differs between regions, with an estimated 75% of the cases of HCV in the United States remaining undiagnosed.[15] In contrast, the diagnosis rate in Sweden is fairly high with an estimated 20% of patients remaining undiagnosed.[16] This, in combination with the virtually complete national coverage of the Swedish registers, makes Sweden a country well-suited for the investigation of the burden of HCV on the welfare system.

Most importantly, the study showed that 43% of the patients with HCV received compensation from the Social Insurance Agency in form of sick leave or disability pension in 2012 compared with 17% of the comparators. In total, the patients with HCV lost an average of 87 extra workdays per year compared with matched comparators. The difference in the number of sick leave days, as well as disability pension, could be explained by the inherent differences between patients with and without HCV infection, with riskier lifestyle and psychiatric disorders being more common in patients in the HCV cohort.[17,18] This could explain the greater frequency of disability pension and higher mean sick leave days noted 5 years before HCV diagnosis. Interestingly, the annual number of days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis. In contrast, there was only an increase of 15 days in the comparator cohort during the 5 year time frame (Figure 3). Thus, despite that patients with HCV started with a higher number of workdays lost, the analysis showed a rapid increase in both mean sick leave and disability pension in the years leading up to HCV diagnosis. In contrast, no such rapid increase was seen for the match comparators. It suggests that patients did most likely experience increased symptoms as the disease progress. This increase in symptoms lead to a greater utilisation of sick leave, as well as more visits to both primary care physicians and specialists until the HCV diagnosis. In addition, after adjusting for psychiatric disease, the difference in sick leave

between the 2 groups remained, thus suggesting that HCV impacts the general health status of patients. It is tempting to hypothesize that earlier diagnosis and treatment of patients with HCV would slow down the increasing need for sick leave and disability pension; however, the present study was not designed to investigate this. Nevertheless, other studies have suggested that earlier treatment benefits both society and the individual patient.[19–21]

In line with previous studies, there was an increase in mean sick leave days noted during the first year of treatment, which is likely due to the side effects associated with the old interferon-based treatment.[22,23] The newly introduced interferon-free regimens for patients with HCV infection have a more favourable safety profile compared with interferon-based regimens.[24] This would most likely reduce the number of sick leave days needed during treatment. The difference between interferon-based and interferon-free regimens will need to be analysed further when data from interferon-free treatments become available in the registers.

One strength of the study was the use of nationwide register data that contained the actual number of days the social insurance pays for per person. This is in contrast to other studies relying on self-reported information, which are more prone to bias. While the data is only as valid as the information entered, the nationwide Swedish registers are considered to be >99% complete. Nationwide large-scale registries allow assessment of subgroup variations and the use of up to 5 matched comparators from the general population.

One main limitation of the study is that patients were identified in the NPR using physician entered diagnoses from inpatient and non-primary outpatient care (previously discussed for this cohort[25]) thus any mistake entering a diagnosis led to misclassification in the study. Another limitation is that the first visit during the study period may not necessary be the first HCV diagnosis given that the specific ICD code for HCV (B18.2 ICD-10) has only been available since 1997, thus the time of diagnosis must be interpreted with caution. As mentioned in the methods, the Social Insurance Agency data only includes sick leave episodes >14 days, as the first episodes are covered by the employer. This will result in an underestimation of the actual number of workdays lost; however, this applies to both cohorts. Interestingly, the main difference in work absence for US employees with HCV was driven by the short-term disability (defined as sick leave between 14 days and 6 months[5,26]), thus suggesting the present study would capture the HCV-mediated impact on sick leave.

Conclusions

To our knowledge, this is the largest study on sick leave and disability pension in patients with HCV to date and the first longitudinal study that investigated this in relation to time of diagnosis. These results indicate that patients with HCV use more sick days and have a higher frequency of disability pension compared with a comparator cohort from the general population. However, whether earlier hepatitis C diagnosis or virologic cure reduces work absence is not addressed by this study and this needs to be further investigated. Finally, the results may be less generalizable to countries where private health insurance is more common.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden. Informed consent is not needed for large registry-based studies in Sweden.[11]

CONSENT FOR PUBLICATION: Not applicable, only aggregated data included in the study. Informed consent is not needed for large registry-based studies in Sweden.[11]

AVAILABILITY OF DATA AND MATERIALS: The datasets generated and/or analysed during the current study where retrieved from the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labor Market studies (LISA) are available for research after ethical approval. The ethical approval for the present study does not allow for sharing data to persons not included in the ethical approval.

COMPETING INTERESTS: M. Lagging has consultancies with AbbVie, Gilead, and MSD/Merck and is a member of the speakers' bureau for AbbVie, Gilead, and MSD/Merck. M. Sällberg is founder and owner of Svenska Vaccinfabriken AB. F. Hansson reports no conflicts of interest. M. Holton is President of Lorimer Enterprises Inc., a company that has consulted for AbbVie. J. Westin has had paid teaching assignments for AbbVie, Gilead, and MSD/Merck. J. Söderholm and J. Kövamees are employees of AbbVie and may hold AbbVie stocks or stock options. K. Büsch was an employee of AbbVie at the time of the study and may hold AbbVie stocks or stock options.

FUNDING: The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data/input analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication.

AUTHOR CONTRIBUTIONS: The concept of the study was designed by KB and JS. FH and KB managed the database. KB, FH, MH, and JS interpreted the data with support from ML, JK, and JW. KB and JS were the major contributors in writing the manuscript. All authors critically revised the manuscript and approved the final version that was submitted.

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Figure legends

Figure 1

Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified HCV population (n=32,021) and matched general population comparators (n=149,688).

HCV=chronic hepatitis C. "0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

Mean total annual number of days of work loss in 2012 in the Swedish register–identified HCV population (n=32,021); among all patients and those with registered sick leave or disability pension.

HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension days. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 3

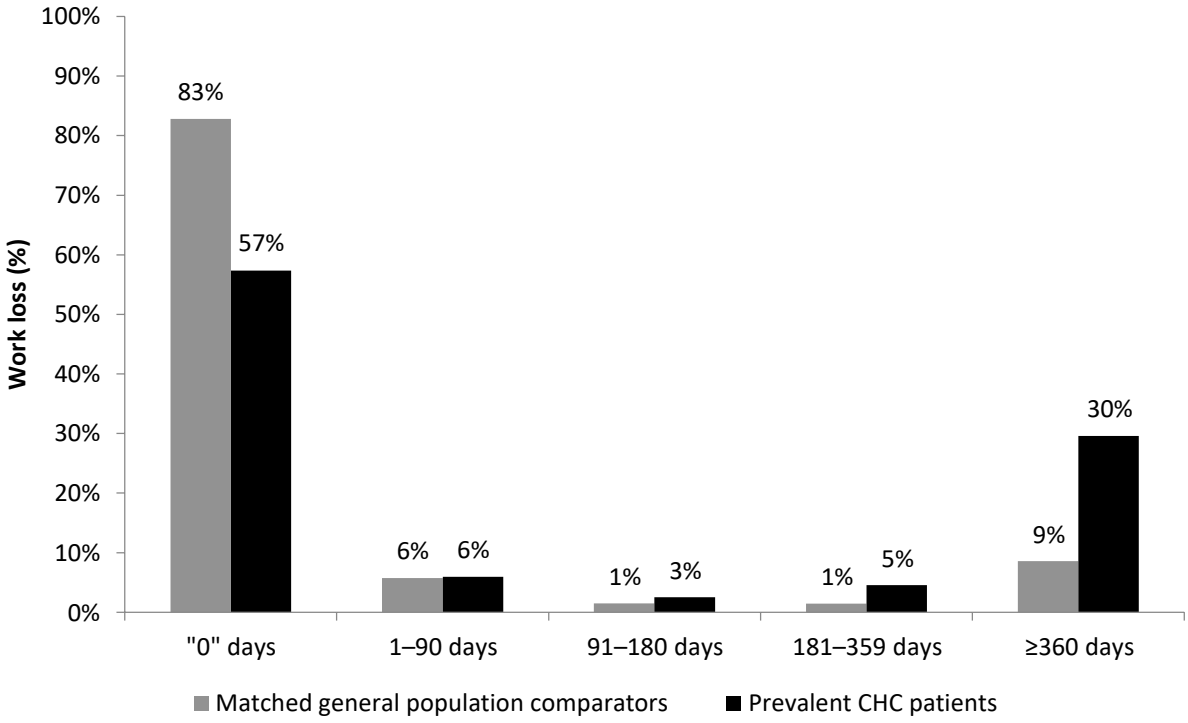
Annual days of sick leave and disability pension 5 years before to 5 years after HCV diagnosis.

Patients with register-identified HCV who were diagnosed between the age of 24 and 59 years (n=19,362) and matched general population comparators (n= 92,697) in a longitudinal analysis of annual days of sick leave and disability pension from 5 years before to 5 years after diagnosis during 1999–2007.

HCV=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population

comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date). The figures show the full distribution of days in categories and annual mean number of total days.

Figure 1 Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified CHC population (n=32,021) and matched general population comparators (n=149,688).



CHC=chronic hepatitis C.

"0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

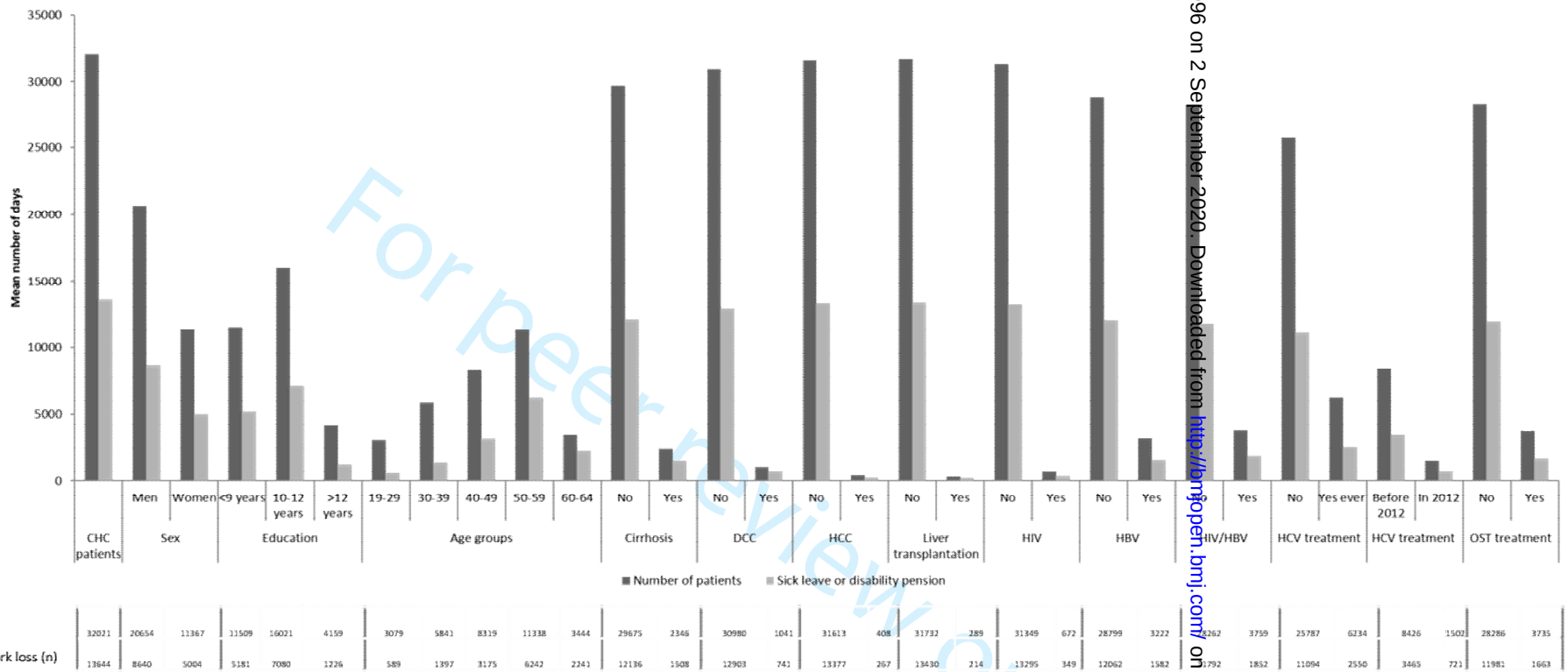


Figure 3

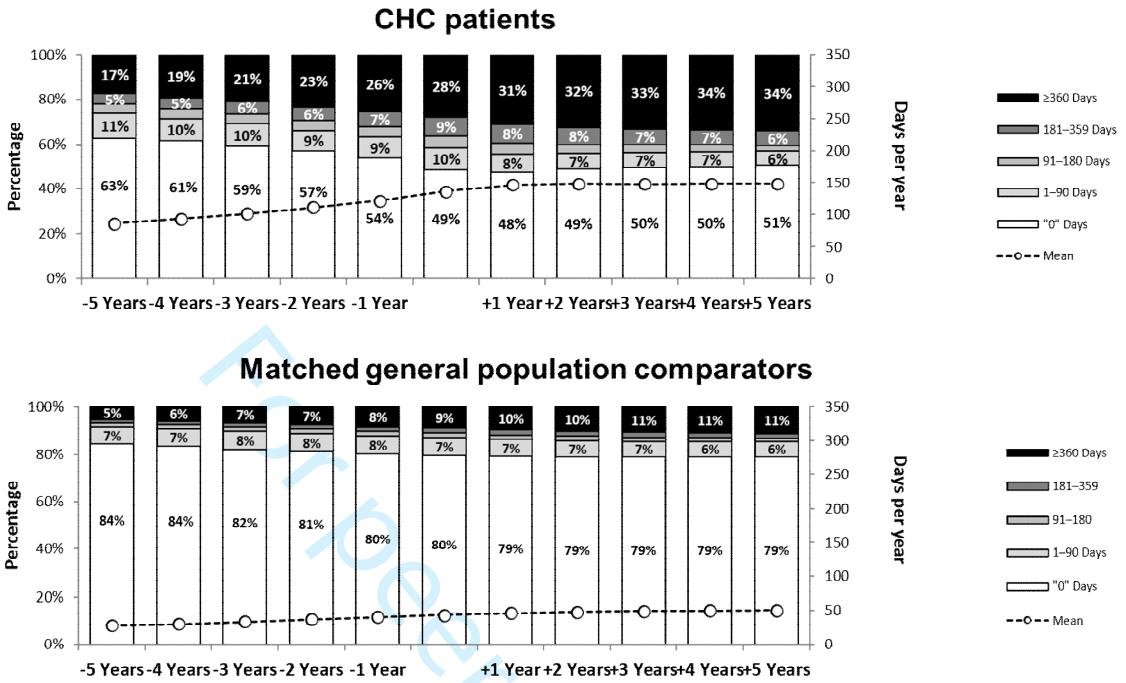
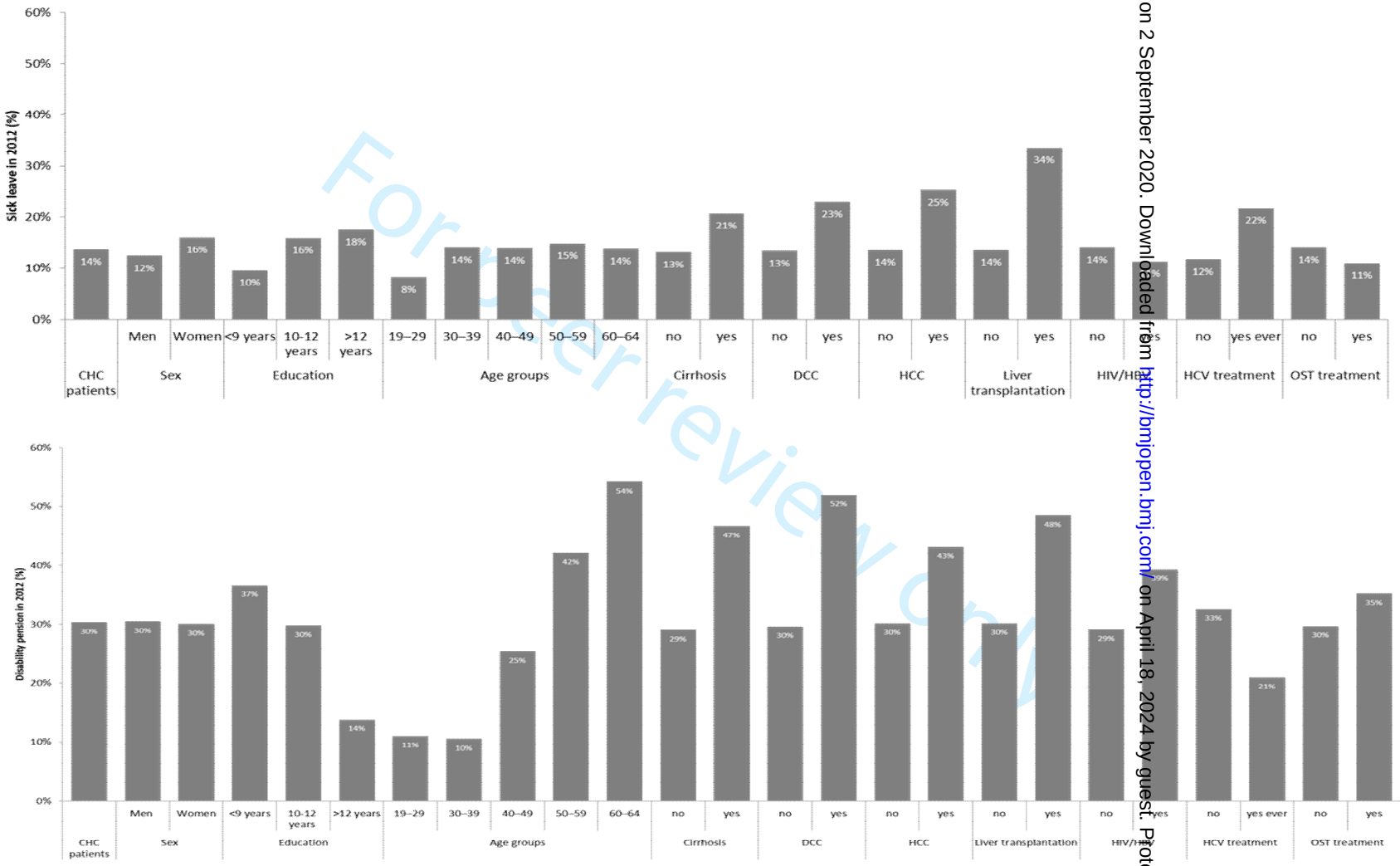
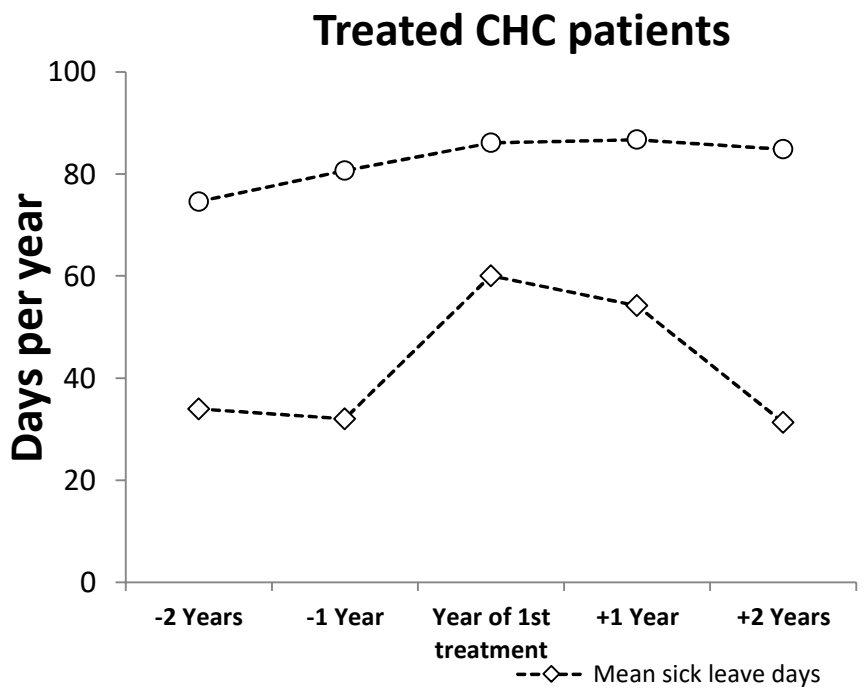


Figure S1 - Proportion of patients on any disability pension or sick leave in 2012 in the Swedish register–identified HCV population (n=32,021).



HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension. Some sick leave episodes ≤14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Figure S2 Mean annual days of sick leave and disability pension in patients with register-identified CHC in a longitudinal analysis from 2 years before to 2 years after first treatment initiation.



CHC=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Supplementary Tables

Table S1 ICD codes used for hepatitis C and liver-related complications

Diseases	ICD9 (1987-1996)	ICD10 (1997-2013)
Hepatitis		
Unspecific/virus hepatitis	070E, 070F, 070G, 070X	B19
Acute hepatitis C	-	B17.1
Chronic hepatitis C	-	B18.2
Chronic active HCV with cirrhosis		*B18.2E*
Chronic HCV with fibrosis		*B18.2F*
Chronic HCV with cirrhosis		*B18.2G*
Liver-related complications / liver disease		
Liver complications*	570, 571A-571G, 571X, 571W, 572C-572E, 572W, 573W	K70, K72, K73, K74, K76
Complication of liver disease	452, 456A-456C	I81, I85, I98.2, I98.3
Symptoms	782E, 789B-789C, 789F	R16, R17, R18,
Hepatocellular carcinoma (HCC)**	155A, 155C, 235D, 239A	C22.0, C22.9, D37.6
Liver transplantation***	V42H	Z94.4

* Plus sub-codes to B18.2E-G (see above); ** Plus ICD7 codes 155.0 in the cancer register; *** Plus surgery codes (see Table S4)

Liver-related complications included liver complications defined fibrosis, cirrhosis, liver failure, complications of the liver defined as portal vein thrombosis, esofageal varices and symptoms including ascites, jaundice.

Table S2 Surgical procedure codes used in the analysis

Surgical procedure	National classification of procedures (till 1996)	NOMESCO classification of surgical procedures (since 1997)
Liver transplantation	5200	JJC

Table S3 ATC codes used in the analysis

Prescribed drugs	**ATC codes (2005-2013)**
Peg-Interferon and ribavirin	J05AB04, L03AB10, L03AB11, L03AB60, L03AB61
Protease inhibitors	J05AE11, J05AE12

Table S4 ICD codes used for co-infections and psychiatric disorders

Diseases	**ICD9 (1987-1996)**	**ICD10 (1997-2013)**
Co-infections		
HIV	279K, 279L	B20-B24
Hepatitis B	070C, 070D	B18.0, B18.1
Other comorbidities		
Psychiatric disorders	F00-F99	290-319

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8

	(e) Describe any sensitivity analyses	Done in ref 2

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Sick leave and disability pension in patients with chronic hepatitis C compared to a matched general population: A nationwide register study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-035996.R2
Article Type:	Original research
Date Submitted by the Author:	23-Jul-2020
Complete List of Authors:	Büsch, Katharina; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine Hansson, Fredrik; Devicia AB Holton, Michelle; Lorimer Enterprises Inc Lagging, Martin ; Goteborgs Universitet, Westin, Johan; Goteborgs Universitet Kövamees, Jan; AbbVie Inc, Medical Affairs Sällberg, Matti; Karolinska Institutet, Department of Laboratory Medicine Söderholm, Jonas; AbbVie Inc, Medical Affairs; Karolinska Institutet, Department of Laboratory Medicine
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Gastroenterology and hepatology, Infectious diseases, Public health
Keywords:	HEALTH ECONOMICS, INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, Gastroenterology < INTERNAL MEDICINE, PUBLIC HEALTH

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Sick leave and disability pension in patients with chronic hepatitis C compared to a matched general population: A nationwide register study

Katharina Büsch[1,2], Fredrik Hansson[3], Michelle Holton[4], Martin Lagging[5], Johan Westin[5], Jan Kövamees[1], Matti Sällberg[2], and Jonas Söderholm[1,2,*]

[1]AbbVie AB, Stockholm, Sweden

[2]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institutet at Karolinska University Hospital Huddinge, Stockholm, Sweden

[3]Devicia AB, Stockholm, Sweden

[4]Lorimer Enterprises Inc., Red Deer, Canada

[5]Department of Infectious Medicine, Institute of Biomedicine, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

Emails: Katharina Büsch, katharina_buesch@yahoo.de; Fredrik Hansson, fredrik.hansson@ctc-ab.se; Michelle Holton, michelle.holton@shaw.ca; Martin Lagging, martin.lagging@medfak.gu.se; Johan Westin, johan.westin@infect.gu.se; Jan Kövamees, jan.kovamees@abbvie.com; Matti Sällberg, Matti.Sallberg@ki.se; Jonas Söderholm, jonas.soderholm@abbvie.com

*__Correspondence__

Jonas Söderholm

Hemvärnsgatan 9

Box 1523, 171 29 Solna, Sweden

Email: jonas.soderholm@abbvie.com; jonas.soderholm@ki.se; Jonas.soderholm@gmail.com

Running title (40 characters without spaces): Sick leave/disability pension in HCV patients

Keywords: Hepatitis C, chronic; Disability Leave; Sick Leave; Sweden

Word Counts, Tables & Figures

Full article: 3,269 words

Abstract: 284 words

Tables: 2

Figures: 3

Supplemental Tables: 3

Supplemental Figures: 1

Abstract

OBJECTIVE: The objective of this study was to evaluate sick leave and disability pension in patients with chronic hepatitis C virus (HCV) infection as compared with a matched general population cohort.

DESIGN: Retrospective register study

SETTING: Nationwide in Sweden

PARTICIPANTS: This register-based study used the Swedish National Patient Register to identify working-age patients with HCV in 2012 (n=32,021) who were diagnosed between 1999 and 2007 (n=19,362). Sick leave and disability pension data were retrieved from Statistics Sweden (1994–2012), with up to 5 matched individuals from the general population.

PRIMARY AND SECONDARY OUTCOME MEASURES: The primary outcome was workdays lost due to sick leave episodes (>14 days) and disability pension overall. The secondary outcome was workdays lost per subgroup of patients with chronic HCV.

RESULTS: In 2012, 14% of the HCV patients had ≥1 registered sick leave episode compared with 10% in the matched comparator cohort. For disability pension benefits, results were 30% vs. 8%, respectively. Overall, in 2012, 57% of patients with HCV did not have any registered workdays lost, whereas 30% were absent ≥360 days compared with 83% and 9% in the matched cohort, respectively. The mean total number of annual workdays lost in 2012 was 126 days in the HCV patient cohort compared with 40 days in the matched general population comparator cohort. Annual days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis.

CONCLUSIONS: These results show that Swedish HCV patients used more sick days and have a higher frequency of disability pension compared with a comparator cohort from the general Swedish population. Whether earlier diagnosis of HCV and treatment might impact work absence in Sweden warrants further investigation.

ARTICLE SUMMARY: Strengths and limitations of the study

- Previous studies focused on describing sick leave in a small segment of patients with chronic hepatitis C, whereas this is the first study to investigating sick leave and disability pension on a nationwide level.

- The registers contain routinely collected data, i.e. limiting the risk for sampling bias.
- The diagnosis analysed was retrieved from Swedish patient register and was not validated, however the Swedish patient register has previously shown high reliability.
- The registers do not contain information on treatment outcome, so analysis on the impact of viral eradication and workdays lost was not feasible.
- The actual number of workdays lost are underestimated since only sick leave episodes ≥14 days are registered.

Background

Hepatitis C is an infectious viral disease affecting the liver, with Western European prevalence rates estimated between 0.35 and 1.42%.[1] In Sweden, the prevalence of chronic hepatitis C infection was estimated to be 0.36% in 2013.[2]

Patients with hepatitis C virus (HCV) infection have been shown to have increased work disabilities.[3] Furthermore, models have shown a relationship between HCV and loss of productivity, increased absenteeism, and higher healthcare benefit costs, which results in substantial economic burden to society.[4–6] A retrospective database analysis showed employees in the United States with HCV infection to have a higher number of lost workdays than employees without HCV infection. In addition, they also utilised more sick leave, with an increased use of short-term and long-term disability.[5] The annual cost due to productivity loss in untreated patients with genotype 1 HCV infection in the United States has been estimated to 7.1 billion USD.[6] Before the introduction of the new interferon-free HCV treatment options the HCV-associated productivity losses in the United Kingdom were estimated to rise from 184–367 million GBP in 2010 to 210–427 million GBP in 2035.[7]

The objective of the present study was to evaluate sick leave and disability pension in patients with chronic HCV compared with matched general population comparators using the Swedish National Patient Register. A secondary objective was to examine sick leave and disability pension within certain subgroups (e.g., patients with decompensated cirrhosis, cirrhosis, hepatocellular carcinoma, or liver transplantation) or prevalent patients, as well as sick leave in relation to diagnosis.

Methods

Setting

The population in Sweden was 9.6 million people in 2012 (Statistics Sweden; www.scb.se). Sweden has a universal tax-funded health care system where the Swedish Social Insurance Agency captures information on full or partial sick leave and disability compensations. In 2012 the common retirement age in Sweden was 65 years with people having the right to retire at 61 years of age or choose to continue working until 67 years of age.

Information on Swedish citizens are collected in the nationwide registers using the Swedish unique personal identity number.[8] In the present study the following registries were used; the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labour Market studies (LISA). The NPR contains

all inpatient (1987–2013) and non-primary outpatient care (2001–2013) visits, but it does not capture any primary care visits.[9] The NPR includes information on both main and contributory diagnoses based on the *International Classification of Diseases* (ICD-9, 1987–1996; ICD-10, 1997-2013). The Cancer Registry covers medical data such as the site of tumour, histologic type, basis, and date of diagnosis (1958–2013). It is mandatory to report all newly detected cancers to the registry. However, some cases are only reported to the CDR (i.e., cases denoted as death certificate only and death certificate notification) and are not necessarily included in the Cancer Registry. The PDR includes all prescribed drug use in ambulatory care (2005–2013), although in-hospital drug use is captured to a much lesser extent.[10] It contains information on dates, drugs, and costs for all pharmacy dispensed prescriptions in Sweden using Anatomical Therapeutic Chemical codes. The CDR contains information on the cause of death with information on the year and month of death. The TPR provides information on place of residence, age, sex, country of origin, and emigration status. LISA includes data on sick leave and disability pension for all residents in Sweden ≥16 years of age with information on work-related and socioeconomic variables (e.g. education level, marital status, and days per year of sick leave and disability pension [annual data retrieved for 1994–2012]).

HCV as a diagnosis was introduced with the ICD-10 in 1997 and at the time of data collection (April 2014) was the data on sick leave and disability pension available until December 31, 2012; thus, the current analysis is based on data from 1997 to 2012.

Informed consent is not required for large-scale registry-based studies in Sweden.[11] Data from the Swedish registries are available for research after ethical and registry approval. The study was approved (Dnr 2014/746-31) by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden.

Patient and Public Involvement

No patient involved.

Identification of patients with HCV and matched general population comparators

Patients were identified in the NPR using health care visits with a chronic HCV diagnosis (ICD10: B18.2),[12] as described previously for this cohort.[2] Only patients of working age (i.e., between 19 and 65 years) were included. Subgroup analyses by age (19–29, 30–39, 40–49, 50–59, 60–65), gender (male/female), education (<9 years, 10–12

years, ≥12 years), disease status (e.g., decompensation cirrhosis [DCC], liver cancer [hepatocellular carcinoma {HCC}], liver transplantation; Table S1 and S2), treatment status (HCV treatment or opioid substitution therapy [OST]; Table S3), and co-infection (HIV or hepatitis B virus; Table S4), were performed. Up to 5 general population controls were matched by age, sex, and county of residence to each patient with HCV at the time of diagnosis.

Definition of outcomes

The outcome was the annual number of days of sick leave and disability pension (maximum of 365 per year).

Sick leave: As of 1998 the first day of sick leave is not compensated ("waiting period") in Sweden, with day 2 to 14 being paid by employers. Thus, only sick leave episodes >14 days were recorded in the LISA database, as those were paid by the Social Insurance Agency. Any episode occurring within 5 days of a previous episode does not require a new "waiting period" or "sick pay period", thus multiple short-term episodes could waive these periods. I.e. individuals with 0 days registered may in fact have had sick leave episodes ≤14 days, hence that group was denoted "0" registered days to acknowledge this uncertainty.

Disability pension: Disability pension refers to either disability pension (1990–2002) or sickness/activity compensation (2003–2012). In Sweden, disability pension can be either part-time (25%, 50%, 67%, or 75%) or full-time (100%) based on the type and severity of the medical condition. As of 2003 was the disability pension replaced by two types of compensation depending on age. "Activity compensation" was introduced for younger individuals (19 to 29 years old) whereas older individuals were eligible for "sickness compensation". Both sickness and activity compensation were either time-limited or permanent but required at least ≥25% reduction in work capacity that was expected for at least 1 year. Gross disability pension refers to the number of days away from work, whereas net disability pension refers to the net time away, e.g. 50% sick leave for 14 days would equal 14 days gross disability pension and 7 days net disability pension (i.e. 182.5 days a year). [13]

Follow-up of patients with HCV and matched general population comparators

Patients with HCV were followed from the date of first visit with an HCV diagnosis during the observation time (index date) until emigration, death, retirement (age 65 years), or study end (December 31, 2012), whichever occurred first. The matched comparators were followed from index date until emigration, death, retirement, until HCV diagnosis, or

December 31, 2012, whichever occurred first. The prevalent cohort included patients alive and living in Sweden as of December 31, 2012.

For the longitudinal analyses of work loss due to sick leave and disability pension the patients with HCV were followed from 5 years before to 5 years after diagnosis. Patients were included if diagnosed between 1999 and 2007 to allow a ±5-year follow-up time. In addition, patients had to be between 24 and 59 years of age at the time of diagnoses in order to be eligible for benefits during the full follow-up. All codes used are available in the supplemental tables S1 – S4.

Statistics

The annual days of sick leave and disability pension were in the descriptive statistics grouped by categories ("0", 1–90, 91–180, 181–359, and ≥360 days) and presented using arithmetic means.[14] The study calculated the total annual number of days of sick leave and disability pension in 2012 for both cohorts. The difference in workdays lost between the groups was also evaluated using multivariable regression models. The analyses were adjusted for age, sex, and educational level, as well as occurrence of psychiatric diseases and/or liver-related outcomes (defined as history of cirrhosis, mental and behavioural disorders, and/or liver transplantation), if the goodness of fit was $R^2>0.6$.

The longitudinal analysis followed the HCV patients and their comparators from 5 years ahead of index date until 5 years after the index date. The impact of interferon-based treatment was analysed for patients with HCV treated with interferon 2 years before until 2 years after first treatment during 2005 and 2010.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. All p values are two-sided.

Results

Overall, 32,021 patients aged 19 to 64 years were diagnosed with HCV and were living in Sweden on December 31, 2012 (HCV prevalent cohort; Table 1).

Table 1 Characteristics of register-identified patients with prevalent HCV aged 19 to 64 years on December 31, 2012, in Sweden and their matched general population comparators

	Patients with HCV in 2012; 19–64 years (n=32,021*)	Matched GenPop comparators in 2012 (n=149,688)
Men, n (%)	20,654 (65%)	95,546 (64%)
Mean (SD) age, y		
At identification/diagnosis	39 (11)	-
In 2012	47 (11)	47 (11)
Highest attained education, n (%)		
<9 years	11,509 (36%)	21,600 (14%)
10–12 years	16,021 (50%)	72,946 (49%)
≥12 years	4159 (13%)	53,866 (36%)
Missing	332 (1%)	1276 (1%)
Marital status at the time of identification, n (%)		

Unmarried	19,725 (62%)	75,011 (50%)
Married	6074 (19%)	57,376 (38%)
Divorced	6111 (19%)	16,539 (11%)
Widow	0	5 (<0.1%)
Missing	111 (0.3%)	757 (1%)
Co-infection, n (%)		
HIV	672 (2%)	210 (0.1%)
HBV	3222 (10%)	377 (0.3%)
Registered HCV -related outcome, n (%)†		
Liver cirrhosis	2346 (7%)	213 (0.1%)
Decompensated cirrhosis	1041 (3%)	31 (0%)
Hepatocellular carcinoma	408 (1%)	125 (0.1%)
Liver transplantation	289 (1%)	48 (<0.1%)
HCV treatment since 2005	6234 (19%)	-
OST treatment since 2005	3735 (12%)	1102 (1%)

HBV=hepatitis B virus; HCV=hepatitis C virus; LISA=Longitudinal Integrated Database for Health Insurance and Labour Market Studies; NPR=National Patient Register; OST=opioid substitution therapy; SD=standard deviation.

*169 patients with HCV were excluded, as there was no data available in the LISA dataset.

†Interpretation of data should be done with caution, as certain outcomes such as liver cirrhosis were likely underreported in the NPR; all codes used to define outcomes are provided in Table S1, S2, S3, and S4.

Prevalence and days of sick leave and disability pension in 2012

Fourteen percent of patients with HCV had ≥1 registered sick leave episode(s) in 2012 compared with 10% in the matched general population comparator cohort. Eight percent of individuals in the matched general population received disability pension benefits, compared with 30% of patients with HCV. In total, 43% of patients with HCV and 17% of individuals in the matched general population comparator cohort had at least one registered sick leave episode or received disability pension benefits in 2012 (Table 2).

Table 2 Annual number of days of sick leave and disability pension in 2012 in patients with register-identified HCV and matched general population comparators

	Patients with HCV in 2012; 19–64 years (n=32,021*)	**Matched GenPop comparators in 2012 (n=149,688)**	**Difference (days)**
Mean (SD) total annual number of days during follow-up	**106 (155)**	**34 (97)**	**72**
Sick leave	27 (78)	13 (55)	14
Disability pension, gross	80 (148)	21 (84)	59
Disability pension, net	76 (143)	18 (75)	58
Mean (SD) total days in 2012	**126 (166)**	**40 (107)**	**86**
Sick leave	22 (72)	11 (88)	11
Disability pension, gross	106 (164)	29 (98)	77
Disability pension, net	101 (159)	25 (88)	76

HCV =chronic hepatitis C; SD=standard deviation.

NOTE. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period (waived only under certain circumstances).

*Matched general population comparators were matched on age, sex, and place of residency at the time of diagnosis.

The proportion of receiving a disability pension was similar among men and women, but was higher among older individuals, those with co-infection (HCV and HIV or hepatitis B virus), and those receiving OST (Figure S1). It was lower among those with a higher educational level and those who previously had been treated for HCV infection. The proportion of sick leave was higher among women and those with higher education, with minor variations by age. Proportion of sick leave or disability pension use was always higher among patients with an HCV–related complication such as cirrhosis, DCC, HCC, or liver transplantation.

Overall, fewer patients with HCV did not have any registered workdays lost in 2012 compared to the matched general population comparator cohort (57% vs. 83%). A greater proportion (30%) of patients with HCV were absent ≥360 days than in the matched general population comparator cohort (9%, p<0.001; Figure 1). The median number of workdays lost was "0" in both cohorts, thus the distribution of workdays lost in 2012 was non-normal.

Among prevalent patients, the annual number of workdays lost was generally higher among older patients, patients with lower education, patients with co-infection, and among patients with liver complications such as DCC, HCC, and liver transplantation (Figure 2). The average total annual number of workdays lost in 2012 was 126 in the HCV patient cohort and 40 in the matched general population comparator cohort (Table 2). When only those with a registered episode were analysed, the mean total annual number of workdays lost rose to 296 days among patients with HCV, a trend that was observed among all subgroups (Figure 2).

The multivariable regression model was adjusted for age, sex, and educational level, showed patients with HCV to have on average 75 more workdays lost compared with the general population. The number of workdays lost decreased to 60 days when considering psychiatric diseases. When also adjusting for any history of either cirrhosis, HCC, or liver transplantation the estimate was reduced to 55 days. The independent factors associated with a greater number of workdays lost were older age, lower level of education, female sex, psychiatric diseases, and history of liver-related outcomes were all independently and significantly (p<0.001).

Longitudinal work loss in relation to diagnosis

Among all patients with HCV 19,362 patients were diagnosed between 1999 and 2007, thus qualified for the longitudinal analysis that followed work loss for up to 5 years before and after diagnosis. Five years before diagnosis,

37% of patients with HCV had workdays lost registered, which increased to 51% in the year of diagnosis and thereafter remained constant. The workdays lost for the matched general population comparators for these 19,362 patients remained between 16% and 21% throughout the longitudinal analysis (Figure 3). More than 30% of patients with HCV were almost fully work disabled already 1 year after diagnosis compared with approximately 10% in the matched general population comparators. Thus, patients with HCV were 3 times as likely to be fully work disabled compared with the matched general population cohort.

The mean annual workdays lost increased from 86 days to 146 days from 5 years before HCV diagnosis to 1 year after diagnosis. The number of workdays lost were always considerably higher among patients with HCV (5 years before HCV diagnosis: 86 vs. 28 days = difference of 59 days; at the year of HCV diagnosis: 136 vs. 43 days = difference of 92 days; 5 years after HCV diagnosis: 148 vs. 50 days = difference of 97 days; Figure 3).

Among the 5,177 patients treated with interferon-based treatments between 2005 and 2010, the mean annual number of sick leave days was approximately 30 days before the start of treatment. Sick leave days increased to 60 days during the year of treatment initiation followed be a decrease to pre-treatment levels (approximately 30 days) 2 years after treatment initiation (Figure S2). No large differences were observed in mean annual disability pension days in relation to interferon-based treatment. The trend that showed an increase in mean disability pension days before treatment initiation was no longer evident after treatment.

Discussion

Hepatitis C infection is a slowly developing disease that often begins with vague symptoms such as fatigue, loss of appetite, and headache. These symptoms often begin to manifest well before the patient is diagnosed with HCV. The comorbidities are believed to affect the general well-being of the patients with an accompanying increased need for sick leave and disability pension. However, the use of sick leave/disability has only been investigated in a few studies, with the largest examining data from 1,664 patients with HCV diagnoses who were employed in the United States. In order to get the full picture of the sick leave and disability pension use for patients with HCV in an entire country and to avoid the bias of only analysing employed patients with HCV, the present study set out to investigating the sick leave and disability pension for all diagnosed patients with HCV of working age in Sweden. The diagnosis rate of HCV differs between regions, with an estimated 75% of the cases of HCV in the United States remaining undiagnosed.[15] In contrast, the diagnosis rate in Sweden is fairly high with an estimated 20% of patients remaining undiagnosed.[16] This, in combination with the virtually complete national coverage of the Swedish registers, makes Sweden a country well-suited for the investigation of the burden of HCV on the welfare system.

Most importantly, the study showed that 43% of the patients with HCV received compensation from the Social Insurance Agency in form of sick leave or disability pension in 2012 compared with 17% of the comparators. In total, the patients with HCV lost an average of 87 extra workdays per year compared with matched comparators. One caveat is that the analysis only included individuals alive as of December 31, 2012 which introduces survivorship bias in both groups. The difference in the number of sick leave days, as well as disability pension, could be explained by the inherent differences between patients with and without HCV infection, with riskier lifestyle and psychiatric disorders being more common in patients in the HCV cohort.[17,18] This could explain the greater frequency of disability pension and higher mean sick leave days noted 5 years before HCV diagnosis. Interestingly, the annual number of days lost increased from a mean of 86 days 5 years before diagnosis to 136 days during the year of diagnosis. In contrast, there was only an increase of 15 days in the comparator cohort during the 5 year time frame (Figure 3). Thus, despite that patients with HCV started with a higher number of workdays lost, the analysis showed a rapid increase in both mean sick leave and disability pension in the years leading up to HCV diagnosis. In contrast, no such rapid increase was seen for the match comparators. It suggests that patients did most likely experience increased symptoms as the disease progress. This increase in symptoms lead to a greater utilisation of sick leave, as well as more visits to

both primary care physicians and specialists until the HCV diagnosis. In addition, after adjusting for psychiatric disease, the difference in sick leave between the 2 groups remained, thus suggesting that HCV impacts the general health status of patients. It is tempting to hypothesize that earlier diagnosis and treatment of patients with HCV would slow down the increasing need for sick leave and disability pension; however, the present study was not designed to investigate this. Nevertheless, other studies have suggested that earlier treatment benefits both society and the individual patient.[19–21]

In line with previous studies, there was an increase in mean sick leave days noted during the first year of treatment, which is likely due to the side effects associated with the old interferon-based treatment.[22,23] The newly introduced interferon-free regimens for patients with HCV infection have a more favourable safety profile compared with interferon-based regimens.[24] This would most likely reduce the number of sick leave days needed during treatment. The difference between interferon-based and interferon-free regimens will need to be analysed further when data from interferon-free treatments become available in the registers.

One strength of the study was the use of nationwide register data that contained the actual number of days the social insurance pays for per person. This is in contrast to other studies relying on self-reported information, which are more prone to bias. While the data is only as valid as the information entered, the nationwide Swedish registers are considered to be >99% complete. Nationwide large-scale registries allow assessment of subgroup variations and the use of up to 5 matched comparators from the general population.

One main limitation of the study is that patients were identified in the NPR using physician entered diagnoses from inpatient and non-primary outpatient care (previously discussed for this cohort[25]) thus any mistake entering a diagnosis led to misclassification in the study. Another limitation is that the first visit during the study period may not necessary be the first HCV diagnosis given that the specific ICD code for HCV (B18.2 ICD-10) has only been available since 1997, thus the time of diagnosis must be interpreted with caution. As mentioned in the methods, the Social Insurance Agency data only includes sick leave episodes >14 days, as the first episodes are covered by the employer. This will result in an underestimation of the actual number of workdays lost; however, this applies to both cohorts. Interestingly, the main difference in work absence for US employees with HCV was driven by the short-term disability

(defined as sick leave between 14 days and 6 months[5,26]), thus suggesting the present study would capture the HCV-mediated impact on sick leave. The main route for HCV transmission in Europe is through the use of non-sterile drug paraphernalia [27] and since drug use is associated with absenteeism [28] it reasonable to think that the higher number of work days lost among patients with HCV is at least partly due to behavioural differences between the groups. However, the study was not designed to address this confounder.

Conclusions

To our knowledge, this is the largest study on sick leave and disability pension in patients with HCV to date and the first longitudinal study that investigated this in relation to time of diagnosis. These results indicate that patients with HCV use more sick days and have a higher frequency of disability pension compared with a comparator cohort from the general population. However, whether earlier hepatitis C diagnosis or virologic cure reduces work absence is not addressed by this study and this needs to be further investigated. Finally, the results may be less generalizable to countries where private health insurance is more common.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE: The study was approved by the Regional Ethics Committee, Karolinska Institutet, Stockholm, Sweden. Informed consent is not needed for large registry-based studies in Sweden.[11]

CONSENT FOR PUBLICATION: Not applicable, only aggregated data included in the study. Informed consent is not needed for large registry-based studies in Sweden.[11]

AVAILABILITY OF DATA AND MATERIALS: The datasets generated and/or analysed during the current study where retrieved from the National Patient Register (NPR), the Cancer Register, the Prescribed Drug Register (PDR), the Cause of Death Register (CDR), the Total Population Register (TPR), and the Longitudinal Integrated Database for Health Insurance and Labor Market studies (LISA) are available for research after ethical approval. The ethical approval for the present study does not allow for sharing data to persons not included in the ethical approval.

COMPETING INTERESTS: M. Lagging has consultancies with AbbVie, Gilead, and MSD/Merck and is a member of the speakers' bureau for AbbVie, Gilead, and MSD/Merck. M. Sällberg is founder and owner of Svenska Vaccinfabriken AB. F. Hansson reports no conflicts of interest. M. Holton is President of Lorimer Enterprises Inc., a company that has consulted for AbbVie. J. Westin has had paid teaching assignments for AbbVie, Gilead, and MSD/Merck. J. Söderholm and J. Kövamees are employees of AbbVie and may hold AbbVie stocks or stock options. K. Büsch was an employee of AbbVie at the time of the study and may hold AbbVie stocks or stock options.

FUNDING: The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the study design, data/input analysis, interpretation of results, review, and approval of the publication. The authors determined the final content. No payments were made to the authors for writing this publication.

AUTHOR CONTRIBUTIONS: The concept of the study was designed by KB and JS. FH and KB managed the database. KB, FH, MH, and JS interpreted the data with support from ML, JK, JW, and MS. KB and JS were the major contributors in writing the manuscript. All authors critically revised the manuscript and approved the final version that was submitted.

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Figure legends

Figure 1

Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified HCV population (n=32,021) and matched general population comparators (n=149,688).

HCV=chronic hepatitis C. "0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

Mean total annual number of days of work loss in 2012 in the Swedish register–identified HCV population (n=32,021); among all patients and those with registered sick leave or disability pension.

HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension days. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 3

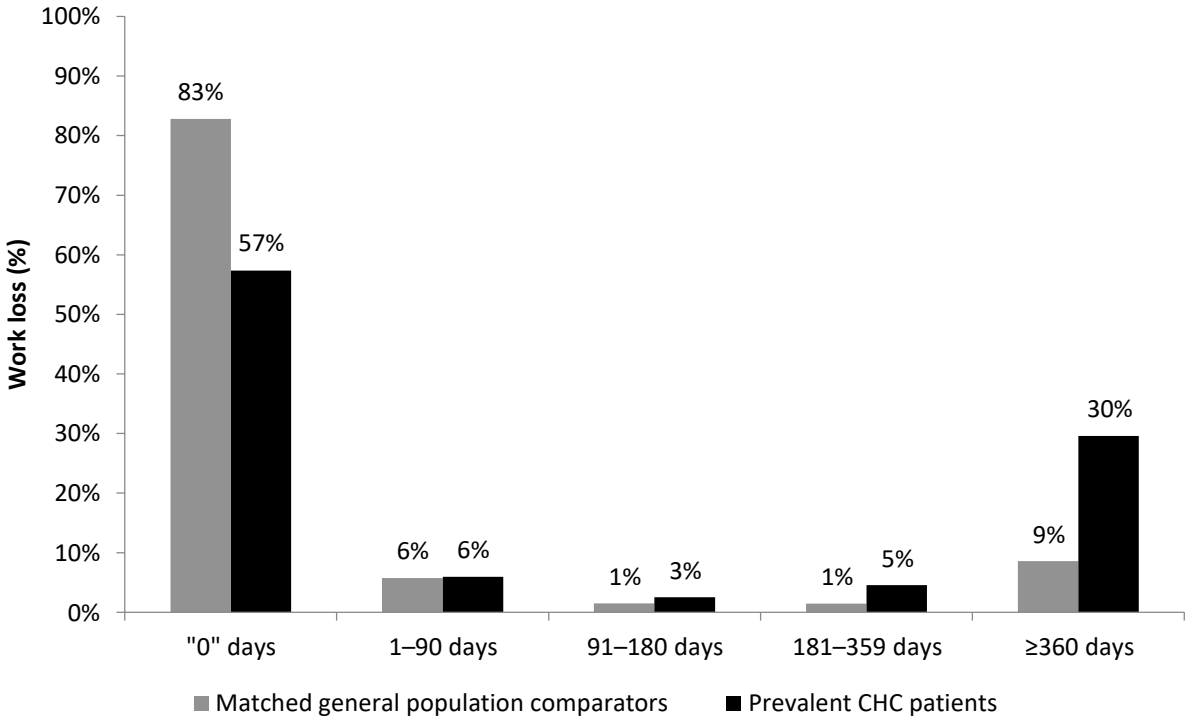
Annual days of sick leave and disability pension 5 years before to 5 years after HCV diagnosis.

Patients with register-identified HCV who were diagnosed between the age of 24 and 59 years (n=19,362) and matched general population comparators (n= 92,697) in a longitudinal analysis of annual days of sick leave and disability pension from 5 years before to 5 years after diagnosis during 1999–2007.

HCV=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances. General population

comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date). The figures show the full distribution of days in categories and annual mean number of total days.

Figure 1 Distribution of days on sick leave and disability pension in 2012 in the Swedish register–identified CHC population (n=32,021) and matched general population comparators (n=149,688).



CHC=chronic hepatitis C.

"0" days may include sick leave episodes <14 days. General population comparators were matched 5:1 by age, sex, and place of residency at the time of diagnosis (index date).

Figure 2

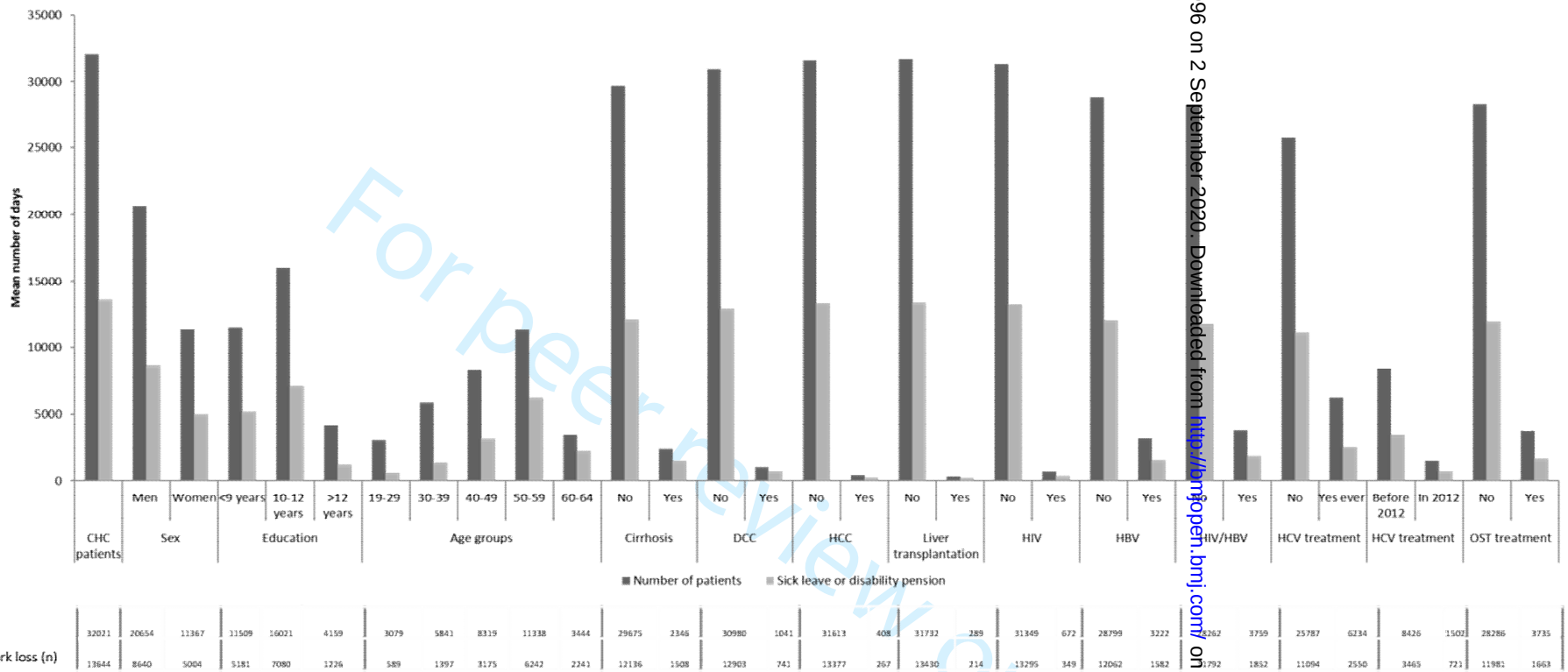


Figure 3

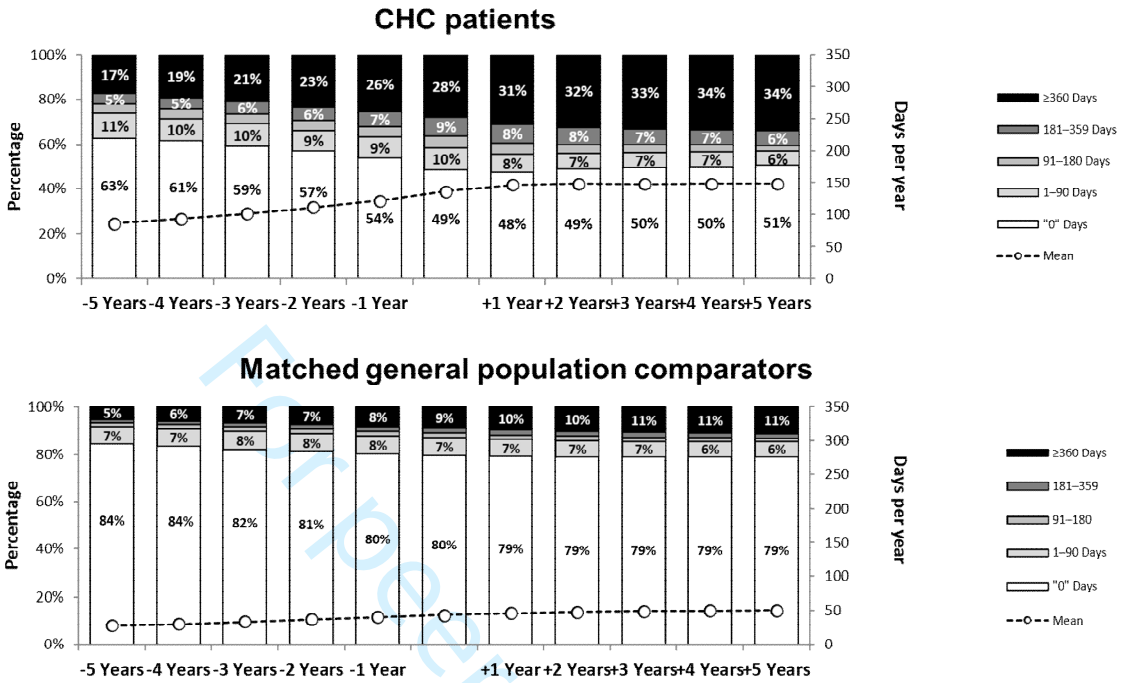
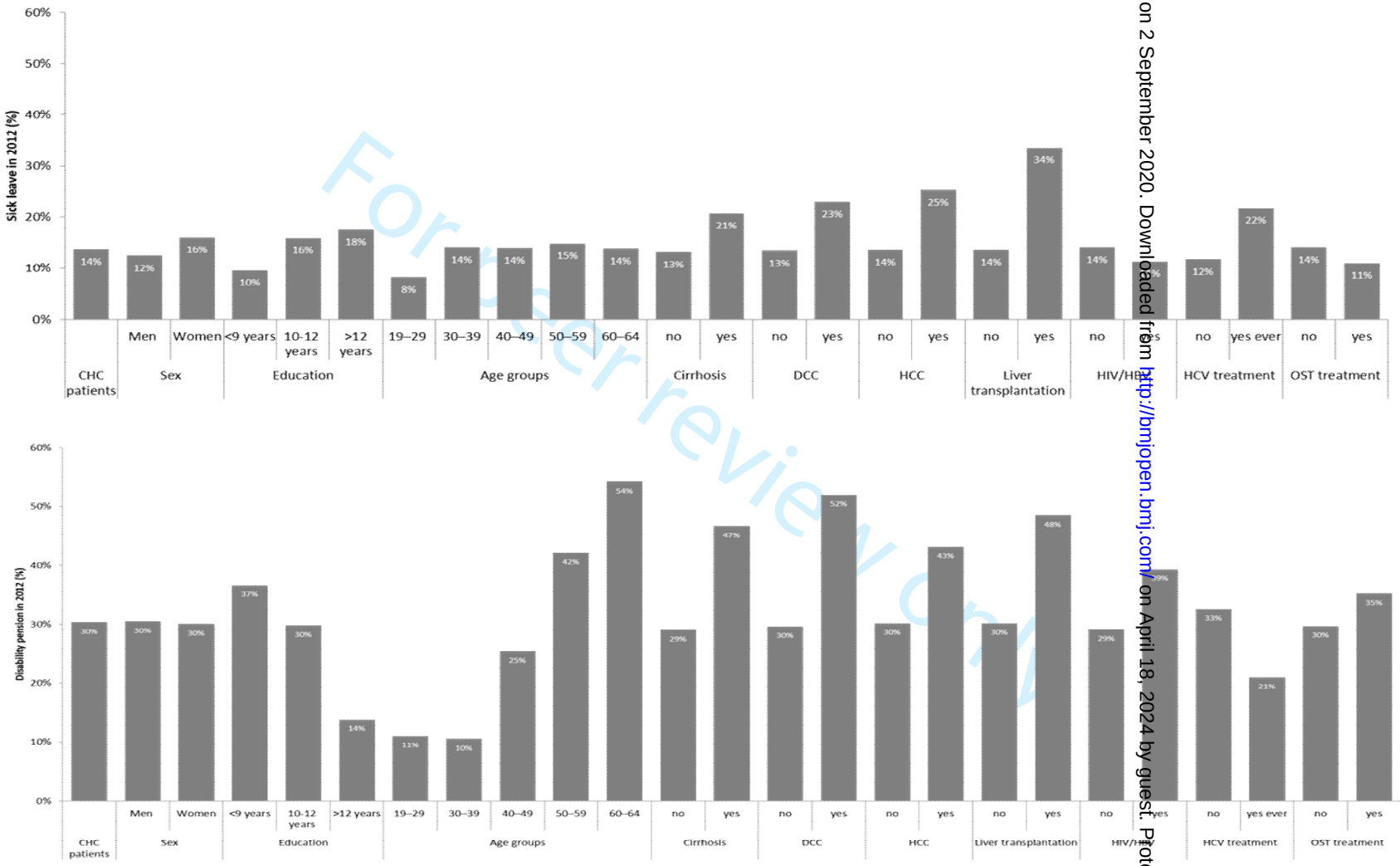
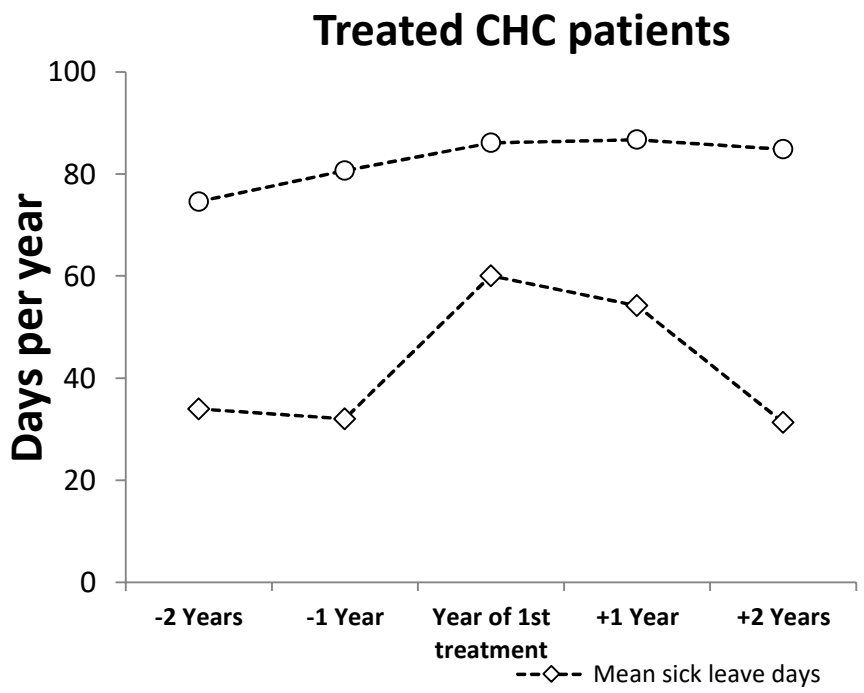


Figure S1 - Proportion of patients on any disability pension or sick leave in 2012 in the Swedish register–identified HCV population (n=32,021).



HCV=chronic hepatitis C; DCC=decompensated cirrhosis; HBV=hepatitis B virus; HCC=hepatocellular carcinoma; HCV=hepatitis C virus; OST=opioid substitution therapy. The bars represent a mix of full-time and part-time sick leave and disability pension. Some sick leave episodes ≤14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Figure S2 Mean annual days of sick leave and disability pension in patients with register-identified CHC in a longitudinal analysis from 2 years before to 2 years after first treatment initiation.



CHC=chronic hepatitis C. Some sick leave episodes <14 days were not captured due to the 1-day waiting period and the 13-day sick pay period, which could be waived only under certain circumstances.

Supplementary Tables

Table S1 ICD codes used for hepatitis C and liver-related complications

Diseases	ICD9 (1987-1996)	ICD10 (1997-2013)
Hepatitis		
Unspecific/virus hepatitis	070E, 070F, 070G, 070X	B19
Acute hepatitis C	-	B17.1
Chronic hepatitis C	-	B18.2
Chronic active HCV with cirrhosis		*B18.2E*
Chronic HCV with fibrosis		*B18.2F*
Chronic HCV with cirrhosis		*B18.2G*
Liver-related complications / liver disease		
Liver complications*	570, 571A-571G, 571X, 571W, 572C-572E, 572W, 573W	K70, K72, K73, K74, K76
Complication of liver disease	452, 456A-456C	I81, I85, I98.2, I98.3
Symptoms	782E, 789B-789C, 789F	R16, R17, R18,
Hepatocellular carcinoma (HCC)**	155A, 155C, 235D, 239A	C22.0, C22.9, D37.6
Liver transplantation***	V42H	Z94.4

* Plus sub-codes to B18.2E-G (see above); ** Plus ICD7 codes 155.0 in the cancer register; *** Plus surgery codes (see Table S4)

Liver-related complications included liver complications defined fibrosis, cirrhosis, liver failure, complications of the liver defined as portal vein thrombosis, esofageal varices and symptoms including ascites, jaundice.

Table S2 Surgical procedure codes used in the analysis

Surgical procedure	National classification of procedures (till 1996)	NOMESCO classification of surgical procedures (since 1997)
Liver transplantation	5200	JJC

Table S3 ATC codes used in the analysis

Prescribed drugs	**ATC codes (2005-2013)**
Peg-Interferon and ribavirin	J05AB04, L03AB10, L03AB11, L03AB60, L03AB61
Protease inhibitors	J05AE11, J05AE12

Table S4 ICD codes used for co-infections and psychiatric disorders

Diseases	**ICD9 (1987-1996)**	**ICD10 (1997-2013)**
Co-infections		
HIV	279K, 279L	B20-B24
Hepatitis B	070C, 070D	B18.0, B18.1
Other comorbidities		
Psychiatric disorders	F00-F99	290-319

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6*
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8

	(e) Describe any sensitivity analyses	Done in ref 2

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*11*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.