

Labour productivity losses caused by premature death associated with hepatitis C in Spain

Juan Oliva-Moreno^a, Luz M. Peña-Longobardo^a, Sonia Alonso^b, Antonio Fernández-Bolaños^a, María Luisa Gutiérrez^b, Álvaro Hidalgo-Vega^a, Elsa de la Fuente^b and Conrado M. Fernández-Rodríguez^b

Background and aims Hepatitis C virus (HCV) infection places a huge burden on healthcare systems. There is no study assessing the impact of HCV infection on premature deaths in Spain. The aim of this study was to estimate productivity losses because of premature deaths attributable to hepatitis C occurring in Spain during 2007–2011.

Materials and methods We use data from several sources (Registry of Deaths, Labour Force Survey and Wage Structure Survey) to develop a simulation model based on the human capital approach and to estimate the flows in labour productivity losses in the period considered. The attributable fraction method was used to estimate the numbers of deaths associated with HCV infection. Two sensitivity analyses were developed to test the robustness of the results.

Results Our model shows total productivity losses attributable to HCV infection of 1054.7 million euros over the period analysed. The trend in productivity losses is decreasing over the period. This result is because of improvements in health outcomes, reflected in the reduction of the number of years of potential productive life lost. Of the total estimated losses, 18.6% were because of hepatitis C, 24.6% because of hepatocellular carcinoma, 30.1% because of cirrhosis, 15.9% because of other liver diseases and 10.7% because of HIV–HCV coinfection.

Conclusion The results show that premature mortality attributable to hepatitis C involves significant productivity losses. This highlights the need to extend the analysis to consider other social costs and obtain a more complete picture of the actual economic impact of hepatitis C infection. *Eur J Gastroenterol Hepatol* 27:631–637
Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

Introduction

Chronic hepatitis C infection represents a huge health burden in various European countries [1], and it is one of the most prevalent chronic viral infections [2], with around 170 million individuals suffering worldwide and an annual rate of increase of three to four million new infections [3]. The WHO estimates that around 3% of the world's population is infected by the hepatitis C virus (HCV), with a prevalence rate ranging from 0.1 to 5% in different European countries [4]. The estimated prevalence of HCV in Spain is 1% (95% confidence interval 0.8–1.3); hence, around 467 000 individuals are viraemic [5].

In Spain, HCV infection is one of the main causes of mortality and morbidity, being the most common cause of cirrhosis [6]. In fact, patients with cirrhosis caused by HCV infection represent almost 50% of those who require liver transplantation and between 70 and 80% of those who have hepatocellular carcinoma (HCC) in Spain [6]. Other studies have analysed the burden of hepatitis B and C, showing the huge impact of these diseases independent of the health outcome considered (premature deaths; years lived with disability; disability adjusted life years) [7]. In fact, hepatitis C was the disease that ranked first in terms of deaths caused by infectious diseases in Spain in 2000, with 44 970 potential years of life lost according to the most conservative estimate [8]. HCV infection underlies 50% of deaths because of cirrhosis, 70% of HCC cases and 20% of deaths in HIV–HCV coinfecting populations in Spain [9].

When evaluating the social impact of a disease, several health-related indicators should be considered to be related directly to the impact caused by health problems on well-being (mortality, mobility, disability and health-related quality of life). In addition to these health outcomes, it is also possible to identify other indicators that can help us to understand better the impact of a disease from a social perspective; one of them is the healthcare cost associated with HCV infection [10–13]. However, studies considering other non-healthcare costs caused by HCV infection are less frequent. Specifically in Spain, data on productivity losses caused by premature deaths associated with HCV infection are lacking. Therefore, the main objective of this work was to generate objective and comparable information on aspects related to loss of labour productivity

European Journal of Gastroenterology & Hepatology 2015, 27:631–637

Keywords: hepatitis C, human capital approach, productivity losses, social costs

^aUniversity of Castilla-La Mancha, Seminar of Research on Economy and Health and ^bService of Gastroenterology, Fundacion Alcorcon University Hospital, University Rey Juan Carlos, Madrid, Spain

Correspondence to Conrado M. Fernández-Rodríguez, MD, PhD, Fundacion Alcorcon University Hospital, University Rey Juan Carlos, Av Valdelaguna-1, 28922-Alcorcon, Madrid, Spain

Tel: +34 91 6219705; fax: +34 91 6219975; e-mail: cfernandez@fhacorcon.es

Received 28 October 2014 **Accepted** 10 February 2015

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.eurojgh.com).

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

caused by premature deaths because of hepatitis C in Spain. Information such as the data described in this study, together with other economic data and data related to healthcare, should be compiled into a body of information to be used by policy makers in deciding the allocation and prioritization of healthcare resources.

Materials and methods

The theoretical framework underlying this study applies human capital models to the field of health [14,15]. Under the human capital approach, an increase in the level of knowledge increases an individual's productivity in the labour market, from which they receive their monetary income, and in the home or nonmarket area. The key element underpinning this model is the dual nature of 'good health'. Good health is desirable for its own sake as carrying out normal activities and enjoying a host of experiences that cannot be purchased depend on our state of health. 'Good health' thus becomes a prerequisite for obtaining and/or maintaining high levels of well-being. Moreover, health can be considered as investment capital as it gains individuals more days of good health, thereby increasing their earning potential. Focusing on this second aspect, negative effects on the health of an individual might result in undesirable effects on productivity at work. According to the human capital theory, the average earnings of a worker are considered to be a reasonable measure of labour productivity. Thus, wages can be used as the basis for estimating labour productivity losses associated with leaving the labour market prematurely as a result of an illness.

Our calculations are based on the average gross wage figures from the Wage Structure Survey of the Spanish National Statistics Institute (S-NSI) [16]. Data on employment were obtained from the Labor Force Survey conducted by the S-NSI in the same years [17]. The employment rate is defined as the percentage of the population that is employed divided by the total working-age population.

Years of potential productive life lost (YPPLL) were calculated from the Death Statistic according to Cause of Death [18], which is also published by the S-NSI. This source provides annual figures on deaths by cause (in accordance with the WHO International Classification of Diseases, 10th ed.).

To not limit the estimates to a single year and to study the progression of the labour impact of premature deaths associated with HCV-related disease, 5 consecutive years were analysed: 2007, 2008, 2009, 2010 and 2011. For this purpose, we applied the attributable fraction (AF) method [8,19–24]. The AF is the difference between the overall average risk of the entire population (both exposed and unexposed individuals) and the average risk in the unexposed, expressed as a fraction of the overall average risk. Thus, one of the most frequent interpretations of the AF is the proportion of disease risk or incidence (premature deaths in our study) that could be eliminated from the population if exposure (to HCV) were eliminated [25].

AF was calculated from the prevalence of HCV infection in some specific underlying diseases such as cirrhosis or HCC, other hepatic diseases and HCV/HIV coinfection [4,24]. Total deaths for each underlying liver disease by sex and age were obtained. Table 1 summarizes the ICD-10 codes that were analysed. The baseline case

Table 1. List of ICD-10 codes included

Classification	ICD-10	Causes
Group 1: hepatitis C	B17.1	Acute hepatitis C
	B18.2	Chronic viral hepatitis C
Group 2: hepatocellular carcinoma	C22.0	Liver cell carcinoma
	C22.7	Other specified carcinomas of liver
	C22.9	Malignant neoplasm of the liver, unspecified
Group 3: cirrhosis	K74.0	Hepatic fibrosis
	K74.1	Hepatic sclerosis
	K74.2	Hepatic fibrosis with hepatic sclerosis
	K74.6	Other and unspecified cirrhosis of the liver
Group 4: other hepatic diseases	B94.2	Sequelae of viral hepatitis
	I85	Oesophageal varices
	K72.1	Chronic hepatic failure
	K72.9	Hepatic failure, unspecified
	K73	Chronic hepatitis not elsewhere classified
	K76.6	Portal hypertension
	R18	Ascites
	R74.0	Elevation of levels of transaminase and lactic acid dehydrogenase
	K76.9	Liver disease, unspecified
	B20–B24	HIV disease
Group 5: HIV–HCV coinfection		

Source: Own elaboration from the ICD-10 codes (Spanish National Statistics Institute).

(scenario 1) occurs when HCC death is 60% attributable, death because of cirrhosis 40% attributable, other hepatic diseases (Table 1) 60% attributable to HCV infection, and HCV/HIV coinfection is attributable to 15% of HIV deaths. Two alternative scenarios were considered (scenarios 2 and 3) with a range of AFs from 70 to 50% for deaths because of HCC, from 50 to 35% for deaths because of cirrhosis, from 70 to 50% for deaths because of other hepatic diseases and from 20 to 10% for deaths because of HIV–HCV coinfection.

With this information, we calculated the number of deaths of working-age individuals. The age limit for workers to remain in the labour market was set at 65 years, which was the legal age of retirement at the time of the study. Once the age of each individual at the time of death and his/her expected gross lifetime wages are known, the present and future flow of productivity lost as a result of premature death for any of the causes under consideration can be calculated. For this purpose, the employment rate and expected earnings were applied to each case, controlling for age and sex up to the predetermined limit of 65 years. In the baseline case, future amounts are discounted at an annual rate of 3% and a rate of annual productivity growth of 1% is applied. In cases of HIV/AIDS deaths, the employment rate for age and sex of HIV–HCV coinfection carriers for whom the most likely transmission route was the use of parenteral drugs was used. This information was obtained from the HIV/AIDS hospital survey for the period 2007–2011. In the remaining cases, the employment rate for age and sex of the Spanish population was used.

In addition, we developed two sensitivity analyses to test the robustness of the results obtained in the baseline case. First, we used the range of AFs considered as scenarios 2 and 3. Second, we re-estimated the results using annual discount rates of 0 and 6% and rates of annual productivity growth of 0 and 2%.

The results of estimations were updated to the year 2011 (base year) using the consumer price index provided by the S-NSI [26].

Results

Between 2007 and 2011, there were 49 335 deaths in Spain attributable to HCV and to diseases directly attributable to this infection. 4128 of all deaths were recorded as because of hepatitis C, 17 059 because of HCC, 16 714 because of cirrhosis, 5864 because of other HCV-associated liver conditions and 5570 because of HIV-HCV coinfection (Table 2). Once risk factors were applied, deaths related to hepatitis C were 25 043 (baseline case); 4128 were directly attributable to hepatitis C, 10 235 to HCC, 6686 to cirrhosis, 3518 to other hepatic conditions and 836 to HIV-HCV coinfection. The highest incidence of death occurred in 2007 (5350 deaths after adjusting for risk attributions) and the lowest occurred in 2011 (4804 deaths) (Table 3).

In terms of working-age deaths (< 65 years), there were 19 889 deaths related to HCV between 2007 and 2011. 1270 of these deaths were recorded because of hepatitis C, 4336 because of HCC, 6796 because of cirrhosis, 2208 because of other HCV-associated liver diseases and 5279 because of HIV-HCV coinfection (Table 2). After adjusting for the attribution of risks, deaths in the population under 65 years decreased to 8707 (baseline case); 1270 of them were directly attributable to hepatitis C, 2602 to HCC 2718 to cirrhosis, 1325 to other hepatic diseases and 792 to HIV/AIDS (Table 3). The highest death incidence in individuals younger than 65 years of age occurred in 2007 (1814 deaths) and the lowest incidence occurred in 2011 (1647 deaths).

Table 2. Results of mortality (without attributable fractions adjustment)

	2007	2008	2009	2010	2011	Total
Total deaths						
Group 1 'Hepatitis C'	860	806	927	809	726	4128
Group 2 'HCC'	3482	3394	3360	3428	3395	17 059
Group 3 'Cirrhosis'	3509	3303	3388	3279	3235	16 714
Group 4 'Other'	1336	1252	1203	1067	1006	5864
Group 5 'HIV-HCV'	1307	1211	1079	1020	953	5570
Total	10 494	9966	9957	9603	9315	49 335
Deaths < 65 years old						
Group 1 'Hepatitis C'	253	240	296	241	240	1270
Group 2 'HCC'	813	854	867	906	896	4336
Group 3 'Cirrhosis'	1441	1396	1345	1330	1284	6796
Group 4 'Other'	515	497	425	401	370	2208
Group 5 'HIV-HCV'	1253	1150	1021	962	893	5279
Total	4275	4137	3954	3840	3683	19 889
YPLL						
Group 1 'Hepatitis C'	3919	3495	4153	3413	3180	18 160
Group 2 'HCC'	8282	8933	9046	9234	8883	44 378
Group 3 'Cirrhosis'	17 351	16 268	15 631	15 273	14 448	78 971
Group 4 'Other'	6683	6472	5185	5113	4785	28 238
Group 5 'HIV-HCV'	27 581	24 731	21 089	19 011	16 976	109 388
Total	63 816	59 899	55 104	52 044	48 272	279 135

Source: Own elaboration from Death Statistic according to Cause of Death (Spanish National Statistics Institute).

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; YPLL, years of potential productive life lost.

The translation of these deaths to YPLL resulted in 279 135 YPLL; 18 160 of these were attributable to hepatitis C, 44 378 to HCC, 78 971 to cirrhosis and 28 238 to other HCV-related hepatic disorders and 109 388 to HIV/AIDS (Table 2). Once the risk factors were applied, YPLL related to hepatitis C decreased sharply to 109 726 (baseline case); 18 160 of these were directly because of hepatitis C, 26 627 because of HCC, 31 588 because of cirrhosis, 16 943 because of other liver disorders and 16 408 because of HIV/AIDS. The year with the highest incidence of YPLL was 2007 (23 975 YPLL), whereas the lowest incidence occurred in 2011 (19 706) (Table 3).

Once correction factors were applied to labour loss attributable to HCV infection (baseline case) between 2007 and 2011, the productivity losses caused by premature deaths associated with hepatitis C in Spain have been estimated at 1054.7 million euros, ranging from 243.4 million euros in 2007 to 177.6 million euros in 2011 (Table 4). Of the total loss estimated, 18.6% were recorded because of hepatitis C, 24.6% because of HCC, 30.1% because of cirrhosis, 15.9% because of other liver diseases and 10.7% because of HIV-HCV coinfection.

Two sensitivity analyses were carried out to observe how the results varied on changing the most relevant parameters of the model. In the first analysis, the rates of attributable risk were modified as described in methods (see Table 1 Supplementary data, Supplemental digital content 1, <http://links.lww.com/EJGH/A21>). According to the percentages of attributable risk described in scenario 2, the labour productivity losses directly or indirectly attributable to hepatitis C between 2007 and 2011 amounted to up to 1243 million euros, ranging from 287.3 million in 2007 to 209.3 million in 2011 (Table 5). 15.8% of the total losses were because of hepatitis C, 24.4% because of HCC, 32% because of cirrhosis, 15.7% because of other hepatic diseases and 12.1% because of HIV-HCV coinfection. Using percentages of attributable risk described in scenario 3, labour losses would increase 906.0 million euros over the entire period analysed, ranging from 208.9 million in 2007 to 152.7 million euros in 2011. 21.7% of the total losses corresponded to hepatitis C, 23.9% to HCC, 30.7% to cirrhosis, 15.4% to other liver diseases and 8.3% to HIV-HCV coinfection.

The discount rates were modified in the second sensitivity analysis (Table 6). Because of the large number of results, we opted to include just the extreme values. Nevertheless, the complete tables of results are available to readers on request. Thus, taking into account the most conservative discount rates (scenario 1), the productivity losses attributable to hepatitis C would be 846.6 million euros, varying between 193.1 million in 2007 and 143.8 million in 2011. Applying less-conservative discount rates (scenario 2), labour losses related to HCV would reach 1418.4 million euros: 334.0 million euros in 2007, 313.5 million euros in 2008, 272.1 million euros in 2009, 263.3 million euros in 2010 and 235.4 million euros in 2011 (Table 6).

Discussion

The results show that the premature mortality attributable to hepatitis C implies major productivity losses. Despite

Table 3. Results of adjusted mortality for attribution fractions

Attribution fractions	Total deaths	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	860	806	927	809	726	4128
60%	Group 2 'Carcinoma'	2089	2036	2016	2057	2037	10 235
40%	Group 3 'Cirrhosis'	1404	1321	1355	1312	1294	6686
60%	Group 4 'Other'	802	751	722	640	604	3518
15%	Group 5 'HIV-HCV'	196	182	162	153	143	836
	Total	5351	5096	5182	4971	4804	25 403
Attribution fractions	Death < 65	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	253	240	296	241	240	1270
60%	Group 2 'HCC'	488	512	520	544	538	2602
40%	Group 3 'Cirrhosis'	576	558	538	532	514	2718
60%	Group 4 'Other'	309	298	255	241	222	1325
15%	Group 5 'HIV-HCV'	188	173	153	144	134	792
	Total	1814	1781	1762	1702	1648	8707
Attribution fractions	YPPLL	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	3919	3495	4153	3413	3180	18 160
60%	Group 2 'HCC'	4969	5360	5428	5540	5330	26 627
40%	Group 3 'Cirrhosis'	6940	6507	6252	6109	5779	31 588
60%	Group 4 'Other'	4010	3883	3111	3068	2871	16 943
15%	Group 5 'HIV-HCV'	4137	3710	3163	2852	2546	16 408
	Total	23 975	22 955	22 107	20 982	19 706	109 726

Own elaboration from Death Statistic according to Cause of Death (Spanish National Statistics Institute).

Table 4. Baseline case estimated productivity losses

Attribution fractions	Productivity losses (baseline case)	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	45.99	41.12	41.23	35.99	32.02	196.36
60%	Group 2 'HCC'	51.50	55.44	51.66	52.73	48.55	259.88
40%	Group 3 'Cirrhosis'	75.47	68.47	60.68	59.59	53.55	317.75
60%	Group 4 'Other'	42.30	40.49	29.07	29.96	25.96	167.78
15%	Group 5 'HIV-HCV'	28.13	25.60	21.52	20.07	17.56	112.87
	Total	243.39	231.12	204.16	196.34	177.64	1054.64

Units: million euros.

Values of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.

Table 5. Sensitivity analysis I (baseline case modifying attribution fractions)

Attribution fractions	Productivity losses	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	45.99	41.12	41.23	35.99	32.02	196.36
70%	Group 2 'HCC'	60.09	64.68	60.27	61.52	56.64	303.20
50%	Group 3 'Cirrhosis'	94.34	85.59	75.84	74.48	66.94	397.19
70%	Group 4 'Other'	49.35	47.24	33.91	34.95	30.29	195.75
20%	Group 5 'HIV-HCV'	37.51	34.13	28.69	26.76	23.41	150.50
	Total	287.28	272.76	239.94	233.70	209.30	1243.00
Attribution fractions	Productivity losses	2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	45.99	41.12	41.23	35.99	32.02	196.36
50%	Group 2 'HCC'	42.92	46.20	43.05	43.94	40.46	216.57
35%	Group 3 'Cirrhosis'	66.04	59.91	53.09	52.14	46.86	278.04
50%	Group 4 'Other'	35.25	33.74	24.22	24.97	21.63	139.82
10%	Group 5 'HIV-HCV'	18.75	17.06	14.35	13.38	11.70	75.25
	Total	208.95	198.03	175.94	170.42	152.67	906.04

Units: million euros.

Values of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.

the significant economic impact described, studies that have analysed the labour costs associated with hepatitis C are rare compared with studies of other diseases such as cancer, cardiovascular, mental or neurodegenerative diseases, where a social perspective (i.e. including not only medical expenses but also other items such as productivity

losses, social services or professional or informal care) is applied more frequently [27–32].

The average productivity loss per HCV premature death is up to 120 000 euros in the period analysed. Comparing this figure with the current treatment cost of HCV in Spain (which may range from 25 700 from 50 400

Table 6. Sensitivity analysis II (baseline case modifying discount rates and the productivity growth rate)

Percentage attribution (baseline case)		Productivity losses (discount rate 6%; productivity growth rate 0%)					
		2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	35.91	32.57	33.19	28.90	25.87	156.44
60%	Group 2 'HCC'	42.25	45.41	42.60	43.69	40.51	214.45
40%	Group 3 'Cirrhosis'	61.00	56.10	49.81	48.77	43.96	259.65
60%	Group 4 'Other'	33.74	31.96	23.37	23.92	20.41	133.40
15%	Group 5 'HIV-HCV'	20.27	18.60	15.80	14.90	13.13	82.70
	Total	193.17	184.64	164.77	160.18	143.88	846.64
Percentage attribution (baseline case)		Productivity losses (discount rate 0%; productivity growth rate 2%)					
		2007	2008	2009	2010	2011	Total
100%	Group 1 'Hepatitis C'	63.96	54.97	54.26	47.73	41.81	262.72
60%	Group 2 'HCC'	68.42	74.07	67.70	67.78	62.01	339.98
40%	Group 3 'Cirrhosis'	100.30	88.49	78.45	77.10	69.22	413.55
60%	Group 4 'Other'	57.57	56.35	39.10	40.86	36.43	230.31
15%	Group 5 'HIV-HCV'	43.75	39.63	32.59	29.92	26.01	171.90
	Total	334.00	313.51	272.10	263.39	235.48	1418.46

Units: million euros.

Values of different years were updated to the reference year (2011). Own elaboration from several sources of Spanish National Statistics Institute.

euros) or with the estimated cost of a liver transplant (above 70 000 euros, only in-patient healthcare resources, excluding the after-treatment monitoring and review), the huge impact that premature deaths have on the total costs attributable to HCV infection is clear. New oral drugs for hepatitis C have completed interferon-free phase III clinical trials and several phase II clinical trials of new interferon-free regimens are ongoing. All these drugs have shown better efficacy in clearing the virus, are better tolerated and require shorter treatments than the current standard of care. Some of these new drugs have recently been approved in the USA and in the EU [33–44]. Many new interferon-free regimens achieve rates of sustained virological response ranging from 88 to 100% [45]. However, the foreseeable scenario for these therapies is uncertain as accessibility to treatment, even in many developed countries, might be restricted [46]. In this sense, not taking account of the nonhealth costs in the economic evaluations of new treatments may have important consequences on the final decision on public financing, pricing and rational use of public resources. In this respect, resources should not be allocated solely according to the burden of a specific disease, but according to where the greatest benefits in terms of health intervention occur; studies on the cost of disease allow to reveal a relevant dimension of a health problem and provide valuable information for society and decision-makers on the relative and absolute importance of the disease and therefore help to design and implement health policies.

Despite the constraints of these types of analysis, governments of many countries and regions continue to promote this work [30] because public decision makers consider information on the economic impact caused by chronic diseases and public-health problems as a valuable tool for the planning and evaluation of their policies [47–49]. However, this information does not replace, but can be complementary to epidemiological data on morbidity and mortality and disabilities caused by a disease. In this sense, cost of illness is one indicator of the consequences of an illness, expressed in monetary terms. These non-healthcare costs are not decorative embellishments in

obscure academic studies. They reflect real burdens that have to be carried by specific individuals or by society [50]. Therefore, the usefulness of a cost study is to identify the economic impact of a particular disease, showing those costs that were not visible or known.

The literature stresses the importance of productivity losses on the total costs attributable to HCV infection, especially those caused by premature mortality, but also those caused by sick leave and presenteeism. For example, Leigh *et al.* [51] analysed healthcare costs and productivity losses in the USA in 1997, estimating that two-thirds of the total costs (5.46 billion dollars) were because of productivity losses. Also, Vietri *et al.* [52], using data from the European National Health and Wellness Survey with patients in France, Germany, UK, Italy and Spain, showed that patients infected with HCV consumed more health resources (19.8 visits to doctors vs. 13.3 for a control group) and suffered more work disability (30 vs. 18%, respectively) and nonwork disability (34 vs. 28%). Work losses were higher, 2956 euros per individual infected with HCV, compared with the control group. The results of other international studies point in the same direction [53–59].

This work has some limitations. The first is that our analysis is based on data provided by the Official Register of Deaths, which in turn relies on death certificates, and HCV infection may be under-reported on death certificates [60]. An ideal study design would be to follow a cohort of HCV patients over an extended period of time using a control group to identify differences in effects on healthcare costs, productivity losses and health indicators. Thus, we would observe the differences in costs (health and nonhealth) and health effects directly instead of applying the method of fractional attributable risk, which may incur bias arising from the presence of multiple risk factors. Nevertheless, the fractional attributable risk approach is epidemiologically oriented, and was chosen in the light of the available data [23].

A second limitation that should be pointed out is the fact that we have used the wages and employment rates in the general population (except for HIV/HCV). Although

some studies did not detect a lower employment rate in some communities with HCV infection [61], it could be argued that IDU is the predominant route of transmission in some countries, and consequently, the employment rate of populations infected by IDU might be lower than the employment rate of the general population. Nevertheless, blood transfusions, intravenous drug use and hospitalizations have been associated independently with HCV infection in Spain [62], and no evidence on the mode of infection could be identified in nearly 40% of HCV [63]. This limitation suggests that more research needs to be developed to gain in-depth knowledge of the labour status (employment and wages) of individuals with HCV.

A third limitation is the failure to include different productivity losses associated with premature death. This work focused on the analysis of labour losses because of premature death. However, there are other productivity losses from temporary or permanent sick leave or as a result of presenteeism that were not analysed because of lack of availability of accessible sources of information. Although chronic hepatitis C infection has traditionally been seen as an asymptomatic process with little impact on daily activities, including work tasks, these patients have impairment in quality of life and present more depression-related symptoms, fatigue or fibromyalgia-like complaints [64]. A future line of work would be to extend the present analysis and perform field work that would estimate the health and nonhealth costs of individuals infected with HCV compared with a well-matched control population.

The theoretical approach used in the study is the human capital theory. This is the most commonly used method to carry out cost-of-illness studies in the health economics literature. However, this method has received some criticisms and there are alternative approaches that can be used for the analyses such as the friction cost method [65]. The methodological differences between the two approaches are discussed in detail in other articles [66–69], and the methodological discussion of the suitability of one method versus the alternative is far from being resolved in the health economics literature [67,70,71]. We will not repeat it here, but it should be noted that the two approaches produce very different results, with lower values in the friction costs method.

In conclusion, this study shows that premature mortality attributable to hepatitis C involves major productivity losses. This type of information should be known to healthcare decision makers in the process of allocation of health resources devoted to the treatment of hepatitis C and its related diseases. Also, economic evaluations of health interventions from a social perspective require the incorporation not only of health costs but also of non-health costs as estimated in this paper.

Future lines of work should address healthcare costs and other social costs, either in cost-of-illness studies of HCV or in economic evaluations of health interventions, thereby allowing us to determine the real economic and social impact of this disease and enabling a more efficient and equitable allocation of resources.

Acknowledgements

The authors thank Sandra Lucia Vidal Perez-Campoamor and María Costi their support and help.

This study was funded by a research grant from Abbvie.

Conflicts of interest

There are no conflicts of interest.

References

- Deuffic-Burban S, Deltenre P, Buti M, Stroffolini T, Parkes J, Mühlberger N, et al. Predicted effects of treatment for HCV infection vary among European countries. *Gastroenterology* 2012; 143:974–985.e14.
- Global Burden Of Hepatitis C Working Group. Global burden of disease (GBD) for hepatitis C. *J Clin Pharmacol* 2004; 44:20–29.
- de Bruijne J, Weegink CJ, Jansen PL, Reesink HW. New developments in the antiviral treatment of hepatitis C. *Vox Sang* 2009; 97:1–12.
- Miebertski N, Schwarzer R, Lettmeier B, Sroczynski G, Zeuzem S, Siebert U. HCV-related burden of disease in Europe: a systematic assessment of incidence, prevalence, morbidity, and mortality. *BMC Public Health* 2009; 9:34.
- Bruggmann P, Berg T, Ovrehus AL, Moreno C, Brandao Mello CE, Roudot-Thoraval F, et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. *J Viral Hepat* 2014; 21 (Suppl 1):5–33.
- Bruix J, Barrera JM, Calvet X, Ercilla G, Costa J, Sanchez-Tapias JM, et al. Prevalence of antibodies to hepatitis C virus in Spanish patients with hepatocellular carcinoma and hepatic cirrhosis. *Lancet* 1989; 2:1004–1006.
- Catalá Lopez F, Alvarez Martín E, Génova Maleras R, Morant Ginestar C. Relationship between research funding in the Spanish National Health System and the burden of disease. *Rev Esp Salud Publica* 2009; 83:137–151.
- García-Ortizarras A, García-Ortuza R, García-Ortuza V. Health investment and the burden of disease because of hepatitis B and C. *Rev Esp Salud Publica* 2009; 83:587–588. author reply 589–591.
- García-Fulgueiras A, García-Piña R, Morant C, García-Ortuza V, Génova R, Alvarez E. Hepatitis C and hepatitis B-related mortality in Spain. *Eur J Gastroenterol Hepatol* 2009; 21:895–901.
- Haj-Ali Saflo O, Hernández Guijo JM. Cost-effectiveness of chronic hepatitis C treatment in Spain. *Gastroenterol Hepatol* 2009; 32:472–482.
- Buti M, Casado MA, Esteban R. Evaluating the cost of sustained virologic response in naive chronic hepatitis C patients treated *à la carte*. *Aliment Pharmacol Ther* 2007; 26:705–716.
- Casado Gómez MA, Alvarez-Rubio L, Miró Manero S, Mariño Hernández EL, Buti Ferret M. Budget impact analysis of the treatment of chronic hepatitis C in a hospital. *Farm Hosp* 2006; 30:291–299.
- Stahmeyer JT, Rossol S, Bert F, Antoni C, Demir M, Hinrichsen H, et al. Cost of treating hepatitis C in Germany: a retrospective multicenter analysis. *Eur J Gastroenterol Hepatol* 2014; 26:1278–1285.
- Grossman M. The demand for health: a theoretical and empirical investigation. National Bureau of Economic Research. Occasional paper 119. New York: Columbia University Press; 1972.
- Grossman M. The human capital model of the demand for health. In: Culyer Ayn JP, editor. *Handbook of health economics*. Amsterdam: North-Holland-Springer-Verlag; 2000.
- Spanish National Statistics Institute. Annual Wage Structure Survey. 2012; Available at: http://www.ine.es/dyngs/INEbase/en/operacion.htm?c=Estadistica_C&cid=1254736061721&menu=ultiDatos&idp=1254735976596. [Accessed 23 December 2014].
- Spanish National Statistics Institute. Economically Active Population Survey. 2014. Available at: http://www.ine.es/dyngs/INEbase/en/operacion.htm?c=Estadistica_C&cid=1254736176918&menu=ultiDatos&idp=1254735976595. [Accessed 23 December 2014].
- Spanish National Statistics Institute. Death statistic according to cause of death. 2012. Available at: <http://www.ine.es/jaxi/menu.do?type=pcaxis&path=%2Ft15/p417&file=inebase&L=1> [Accessed 23 December 2014].
- Garcereza-Baziras A, Garcereza-B R, Morant C, de Larrea-Baz NF, Alvarez E. Burden of disease related to hepatitis C and hepatitis B in Spain: a methodological challenge of an unfolding health problem. *J Viral Hepat* 2011; 18:e453–e460.
- Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006; 45:529–538.
- Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology* 2005; 42:711–723.

- 22 Degos F, Christidis C, Ganne-Carrie N, Farmachidi JP, Degott C, Guettier C, *et al.* Hepatitis C virus related cirrhosis: time to occurrence of hepatocellular carcinoma and death. *Gut* 2000; 47:131–136.
- 23 Steenland K, Armstrong B. An overview of methods for calculating the burden of disease due to specific risk factors. *Epidemiology* 2006; 17:512–519.
- 24 Miettinen OS, Miettinen OS, Alexander HE, Leidy G, Hahn E. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 1974; 99:325–332.
- 25 Levine B. What does the population attributable fraction mean? *Prev Chronic Dis* 2007; 4:A14.
- 26 Spanish National Statistics Institute. Consumer Price Index. 2014; Available at: <http://www.ine.es/jaxi/menu.do?type=pcaxis&path=%2Ft25/p138&file=inebase&L=1>. [Accessed 23 December 2014].
- 27 Akobundu E, Ju J, Blatt L, Mullins CD. Cost-of-illness studies: a review of current methods. *Pharmacoeconomics* 2006; 24:869–890.
- 28 Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. *Eur Heart J* 2006; 27:1610–1619.
- 29 Oliva-Moreno J, Liva-Moreno J, Montejo-Gonzalez AL, Osuna-Guerrero R, Duque-Gonzalez B. The socioeconomic costs of mental illness in Spain. *Eur J Health Econ* 2009; 10:361–369.
- 30 Naci H, Fleurence R, Birt J, Duhig A. Economic burden of multiple sclerosis: a systematic review of the literature. *Pharmacoeconomics* 2010; 28:363–379.
- 31 Luengo-Fernandez R, Leal J, Gray AM. Cost of dementia in the pre-enlargement countries of the European Union. *J Alzheimers Dis* 2011; 27:187–196.
- 32 Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. *Lancet Oncol* 2013; 14:1165–1174.
- 33 Dhaliwal HS, Nampoothiri RV. Daclatasvir plus sofosbuvir for HCV infection. *N Engl J Med* 2014; 370:1560.
- 34 Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, *et al.* Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; 370:1889–1898.
- 35 Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, *et al.* ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med* 2014; 370:1973–1982.
- 36 Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, *et al.* Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; 370:1879–1888.
- 37 Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, *et al.* Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; 370:1993–2001.
- 38 Sulkowski MS, Jacobson IM, Nelson DR. Daclatasvir plus sofosbuvir for HCV infection. *N Engl J Med* 2014; 370:1560–1561.
- 39 Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlidne M, *et al.* Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370:1604–1614.
- 40 Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, *et al.* Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; 368:1878–1887.
- 41 Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, *et al.* Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; 368:1867–1877.
- 42 Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, *et al.* Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med* 2014; 370:1594–1603.
- 43 Zeuzem S, Soriano V, Asselah T, Bronowicki JP, Lohse AW, Müllhaupt B, *et al.* Faldaprevir and deleobuvir for HCV genotype 1 infection. *N Engl J Med* 2013; 369:630–639.
- 44 Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, *et al.* Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014; 383:515–523.
- 45 Schinazi R, Halfon P, Marcellin P, Asselah T. HCV direct-acting antiviral agents: the best interferon-free combinations. *Liver Int* 2014; Suppl 1 (Suppl 1):69–78.
- 46 Pawlowsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology* 2014; 146:1176–1192.
- 47 Hu J, Meek P. Health-related quality of life in individuals with chronic obstructive pulmonary disease. *Heart Lung* 2005; 34:415–422.
- 48 Sachs J. *Macroeconomics and health: Investing in health for economic development Report of the Commission on Macroeconomics and Health Geneva*. Switzerland: World Health Organization; 2001.
- 49 Shurcke M, Mckee M, Sauto-Arce R, Tsolova S, Mortensen J. *The contribution of health to the economy in the European Union European Communities*. Luxembourg: Office for Official Publications of the European Communities; 2005.
- 50 Knapp M. Hidden costs of mental illness. *Br J Psychiatry* 2003; 183:477–478.
- 51 Leigh JP, Bowlus CL, Leistikow BN, Schenker M. Costs of hepatitis C. *Arch Intern Med* 2001; 161:2231–2237.
- 52 Vietri J, Prajapati G, El Khoury AC. The burden of hepatitis C in Europe from the patients' perspective: a survey in 5 countries. *BMC Gastroenterol* 2013; 13:16.
- 53 Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am J Public Health* 2000; 90:1562–1569.
- 54 Patrui B, Nolte E. *Hepatitis C A projection of the healthcare and economic burden in the UK*. Cambridge, UK: RAND Corporation; 2013. p. 58.
- 55 Shiell A, Law MG. The cost of hepatitis C and the cost-effectiveness of its prevention. *Health Policy* 2001; 58:121–131.
- 56 Su J, Brook RA, Kleinman NL, Corey-Lisle P. The impact of hepatitis C virus infection on work absence, productivity, and healthcare benefit costs. *Hepatology* 2010; 52:436–442.
- 57 Manne V, Sassi K, Allen R, Saab S. Hepatitis C and work impairment: a review of current literature. *J Clin Gastroenterol* 2014; 48:595–599.
- 58 daCosta DiBonaventura M, Yuan Y, Wagner JS, L'Italien GJ, Lescauwat B, Langley P. The burden of viral hepatitis C in Europe: a propensity analysis of patient outcomes. *Eur J Gastroenterol Hepatol* 2012; 24:869–877.
- 59 DiBonaventura MD, Yuan Y, Lescauwat B, L'Italien G, Liu GG, Kamae I, Mauskopf JA. Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey. *PLoS One* 2014; 9:e86070.
- 60 Mahajan R, Xing J, Liu SJ, Ly KN, Moorman AC, Rupp L, *et al.* Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHCS), 2006–2010. *Clin Infect Dis* 2014; 58:1055–1061.
- 61 Rodriguez AE. Risk factors and associations for hepatitis C infection among Hispanic/Latino intravenous drug users in Miami-Dade County, Florida [dissertation]. Miami: Florida International University; 2012. Available at: <http://digitalcommons.fiu.edu/cgi/viewcontent.cgi?article=1857&context=etd>. [Accessed 23 February 2015].
- 62 Domlerasz A, Bruguera M, Vidal J, Plans P, Salleras L. Community-based seroepidemiological survey of HCV infection in Catalonia, Spain. *J Med Virol* 2001; 65:688–693.
- 63 Sacristil B, Gastastilla MI, Elena A, Sacristil M, Barcenilla J, Garcen JC, Yangelil J. Seroepidemiologic study of hepatitis C virus infection in a general population from the region of La Rioja, Spain. *Med Clin (Barc)* 1996; 107:331–335.
- 64 Mohammad A, Carey JJ, Storan E, Scarry M, Coughlan RJ, Lee JM. Prevalence of fibromyalgia among patients with chronic hepatitis C infection: relationship to viral characteristics and quality of life. *J Clin Gastroenterol* 2012; 46:407–412.
- 65 Koopmanschap MA, Rutten FF, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *J Health Econ* 1995; 14:171–189.
- 66 Johannesson M, Karlsson G. The friction cost method: a comment. *J Health Econ* 1997; 16:249–255. discussion 257–259.
- 67 Liljas B. How to calculate indirect costs in economic evaluations. *Pharmacoeconomics* 1998; 13 (Pt 1):1–7.
- 68 Oliva-Moreno J. Loss of labour productivity caused by disease and health problems: what is the magnitude of its effect on Spain's economy? *Eur J Health Econ* 2012; 13:605–614.
- 69 Krol M, Brouwer W, Rutten F. Productivity costs in economic evaluations: past, present, future. *Pharmacoeconomics* 2013; 31:537–549.
- 70 Zhang W, Bansback N, Anis AH. Measuring and valuing productivity loss due to poor health: a critical review. *Soc Sci Med* 2011; 72:185–192.
- 71 Nyman J. Productivity costs revisited: toward a new US policy. *Health Econ* 2012; 21:1387–1401.