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Real-World Economic Burden of Hepatitis C and Impact of Direct-Acting

Antivirals in France: A Nationwide Claims Data Analysis

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Abbreviations

CI, confidence interval; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LTD, long-term disease; SNDS, Système National des Données de Santé (French administrative health care database).

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aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Ethics Approval Statement and Patient Consent Statement

French decree no. 2021-848 granted the authors permanent access to the SNDS.

The study adhered to the principles of the Declaration of Helsinki and French law on biomedical research and was approved by INSERM CepiDC. All data were anonymized, and no informed consent was obtained for the SNDS analysis.

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Abstract

Background & Aims: The economic impact of managing patients with hepatitis C virus (HCV) infection remains unknown. This study aimed to assess the economic burden of chronic HCV infection from a national health insurance perspective and the impact of direct-acting antivirals (DAAs) using nationwide real-world data.

Methods: Patients with chronic HCV infection were identified from the French Health Insurance Claims Databases (SNDS) and matched for age and sex to the general population. Health resource utilization and reimbursements were summarized according to healthcare expenditure items from 2012 to 2021. The economic burden attributable to chronic HCV infection was evaluated over a 10-year period. Finally, the impact of DAAs was estimated using economic data derived from the SNDS.

Results: A total of 145,187 patients with chronic HCV infection were identified. Among the patients eligible for DAA therapy, 81.5% had received DAA by the end of 2021. Over a 10-year period, managing patients with chronic HCV infection resulted in an additional cost of €9.71 billion (95% confidence interval [CI]: €9.66–€9.78 billion) or €9,191 (95% CI: €9,134–€9,252) per patient per year compared to the general population. After DAA therapy, patients with chronic HCV infection had a higher economic burden than the general population, with an additional cost of €5,781 (95% CI: €5,540–€6,028) per patient at the fifth year post-DAA therapy.

Conclusions: A significant economic burden persists among patients with HCV infection after DAA treatment. The high proportion of patients not treated with DAA therapy supports reinforcing policies for universal access.

Keywords: Health Care Costs; Antiviral Agents; Hepatitis C; Chronic; Administrative Claims; Healthcare.

Lay Summary - Key Points

- The economic burden of chronic Hepatitis C virus (HCV) infection and the impact of direct-acting antivirals (DAAs) have not been evaluated nationally using extensive real-world data from French claims databases.
- Our results showed a significant and persistent economic burden even after successful treatment with DAAs, underscoring the necessity for ongoing efforts to develop strategies to mitigate this persistent burden in patients with chronic HCV infection.
- Given the large number of patients not treated with DAAs, policies promoting universal access to DAAs must be strengthened to achieve HCV viral eradication.

Introduction

The clinical management of patients with chronic hepatitis C virus (HCV) infection aims to limit the progression of liver fibrosis, liver-related complications, and the extrahepatic burden associated with HCV infection.¹ To this end, direct-acting antivirals (DAAs) have been proven effective in reducing liver complications and mortality and achieving sustained virologic response. Consequently, a universal access policy for DAAs was implemented in France in 2017 owing to their proven efficacy and tolerability.^{2,3}

Nevertheless, universal access to DAAs could result in a significant economic burden and threaten the long-term sustainability of healthcare systems, given the large number of patients chronically infected with HCV and the high cost of these medications.⁴ To evaluate this burden, it is imperative to evaluate the health resource utilization associated with managing patients with chronic HCV infection in the DAA era and perform a comprehensive assessment from the national health insurance perspective.

Previous economic models assessing the budgetary impact and cost-effectiveness of DAAs in France had several limitations, including relying on input parameters from clinical trials performed in selected patients with chronic HCV infection or studies not conducted in the French setting.^{5,6} In addition, most models focused on the cost-effectiveness of specific DAA regimens rather than examining the overall impact of DAAs on the economic burden of hepatitis C in France.^{5,7} Furthermore, it is essential to gather updated data on the actual proportion of patients who received DAA therapy in the national cohort of patients with chronic HCV infection to identify future efforts to achieve the HCV elimination goal set for France in 2025.⁸

The French national claims databases are a valuable resource for estimating the real-world economic burden of chronic HCV infection and the impact of DAA regimens.⁹ In this study, we examined reimbursement data from the French health insurance claims databases (SNDS) to estimate the economic burden of chronic HCV infection from 2012 until the end of 2021. Additionally, we evaluated the proportion of patients with chronic HCV infection treated with DAAs and the impact of DAA therapy on healthcare resource utilization from a national health insurance perspective.

Patients and methods

Study design and population

We analyzed the SNDS from January 1, 2010, to December 31, 2021, to identify patients with chronic HCV infection. A multi-criteria algorithm was used to identify a national cohort of patients with chronic HCV infection in France. This algorithm was previously validated using the reference viral hepatitis status as defined in the data from hepatitis B virus (HBV)- or HCV-infected patients enrolled between August 2012 and December 2015 in the French hepatology centers (ANRS CO22 HEPATHER) cohort.¹⁰ It combines various criteria related to chronic HCV infection management, including notification of long-term diseases (LTD, which refers to any severe or costly illness that entitles the patient to full reimbursement of medical expenses), hospital stay, medications related to HCV infection, laboratory tests, and medical procedures. This multi-criteria algorithm revealed a sensitivity of 96% and a specificity of 85%, with the viral status of patients from the ANRS CO22 HEPATHER cohort used as the gold standard. Of note, the specificity was calculated using HBV-infected patients as the control group.

To compare the economic data of individuals with chronic HCV infection with those of the general population, we randomly selected a sample of more than 5.5 million individuals without HCV infection from the SNDS. The cohort of patients with chronic HCV infection aged 18–85 years was then matched 1:1 to individuals from the general population based on birth year and sex to estimate the costs attributable to chronic HCV infection and its associated comorbidities. Patients with chronic HCV infection were matched with individuals from the general population on the date of entry into the cohort to adjust for potential changes in management and healthcare costs over time. All identified individuals were analyzed from January 1, 2012, to December 31, 2021 (Fig. 1).

Data sources

The primary data source was reimbursement data from French claims databases known as the SNDS (système national des données de santé).¹¹ The SNDS covers over 99% of the French population and includes extensive reimbursement data related to inpatient and outpatient hospitalizations, dispensed medications, medical procedures, and laboratory diagnostic tests. Additionally, it provides data on LTD and the date of death.

Covariates and outcomes

Reimbursement data were examined from January 1, 2012, to December 31, 2021. These included direct and indirect medical expenses reimbursed by the French National Health Insurance in both outpatient and inpatient settings, such as hospital stays in public and private institutions, medications dispensed in retail or hospital pharmacies (including expensive medications such as DAAs prescribed during the prioritized access period), medical devices, medical procedures, ambulatory laboratory tests, disability pensions, physician visits, transportation, work-related

accidents, and occupational diseases. Baseline characteristics of the patients were established using specific International Classification of Diseases 10th Revision (ICD-10) codes in the SNDS, as shown in Supplementary Table 1.

Assessment of the economic impact of DAA

The proportion of patients who received DAA therapy and the changes over time were estimated by determining the annual number of patients eligible for DAA therapy and those treated with DAAs. Owing to the unavailability of laboratory test results in the French claims database, the following conditions were used to define patients eligible for DAA therapy each year: 1) being identified as a patient with chronic HCV infection in the French claims database based on the previously described validated multi-criteria algorithm; 2) being alive during the respective year; 3) no previous treatment with DAAs; and 4) no evidence of cure with interferon and ribavirin; that is, patients treated with interferon and ribavirin and not retreated with DAAs over the study period were considered as biologically cured patients and were not deemed eligible for DAA therapy. We identified all dispensed DAAs using specific medication codes for DAA regimens, including those obtained from ambulatory and hospital pharmacies (Supplementary Table 2).

Changes in medical expenses before and after DAA therapy were estimated, and the annual reimbursement per patient with chronic HCV infection was summarized over the consecutive years pre- and post-DAA therapy. The average reimbursement per individual for the matched general population was deduced from the overall economic burden to evaluate the specific burden attributable to chronic HCV infection management.

Ethics statement

French decree no. 2021-848 granted the authors permanent access to the SNDS.

The study adhered to the principles of the Declaration of Helsinki and French law on biomedical research and was approved by INSERM CepiDC. All data were anonymized, and no informed consent was obtained for the SNDS analysis.

Statistical analyses

Aggregated reimbursement data were descriptively summarized annually according to 12 healthcare expenditure categories. Specific reimbursements per person per year were calculated for patients with chronic HCV infection and the general population. The confidence intervals (CIs) were estimated using a bootstrap approach (10,000 iterations). For all patients with chronic HCV infection, follow-up began on the date of the first recorded evidence of the disease in the SNDS and continued until the date of death or 12/31/2021, whichever occurred first. All analyses were performed using the R version 4.1.2 (R Core Team).

Public and patient involvement

There was no public or patient involvement in the design of this study. All data collected from the SNDS were anonymized, and the study results were not intended for direct dissemination to the study participants.

Role of the funding source

The funding source was not involved in the study design, data collection and analysis, report writing, or decision to submit the paper for publication.

Results

Participants

In the French claims databases, we identified 145,187 patients who received care for chronic HCV infection between January 1, 2010, and December 31, 2021 (Fig. 1).

After excluding patients with an uncertain date of birth or death, 145,038 patients

with chronic HCV infection were included. Of these, 141,141 were individually matched to a random cohort of the general population by sex and year of birth. The median age of the individuals was 52 years (interquartile range [IQR]: 45–60 years), and 61% were male (Supplementary Table 3). The total follow-up period analyzed in this study was 2,205,476 person-years, with a median follow-up time of 10 years (IQR: 7–10 years).

Economic burden of chronic HCV infection

Over 10 years, the cumulative amount reimbursed for the management of chronic HCV infection was €11.93 billion (95% CI: 11.87–11.99 billion), with an average reimbursement of €11,129 (95% CI: 11,069–11,185) per patient per year (Supplementary Table 4). Contrastingly, the total expenditure for the general population between January 1, 2012, and December 31, 2021, was €2.22 billion (95% CI: 2.21–2.23 billion). Therefore, the additional cost attributable to the management of chronic HCV infection was €9.71 billion (95% CI: €9.66–€9.78 billion) (Table 1). The additional cost per patient with chronic HCV infection compared with the matched general population cohort was €9,191 (95% CI: €9,134–€9,252) per year.

Fig. 2 details the changes in reimbursements for chronic HCV infection over time according to the main categories of healthcare expenditure. Medication expenditures increased by 135% between 2013 and 2015 before gradually decreasing until 2021. Medication-related reimbursement was the primary driver of healthcare costs for patients with chronic HCV infection. Reimbursements related to expensive medications increased by seven-fold between 2013 and 2015. In 2012, 2015, and 2021, medication expenditures represented 57%, 72%, and 46% of the total reimbursement for the management of chronic HCV infection, respectively. The

proportion of healthcare expenditures associated with hospital stays remained unchanged between 2012 and 2021.

The economic impact of DAA therapy

Fig. 3 illustrates the changes in reimbursements for chronic HCV infection before and after DAA therapy. The total amount reimbursed per patient with chronic HCV infection increased significantly, by more than six-fold (516%), from the year preceding DAA therapy to the year of DAA initiation, reaching €46,439 (95% CI: €46,193–€46,677) per patient (Supplementary Table 5). Notably, the healthcare reimbursements per patient with chronic HCV infection were €7,533 (95% CI: €7,342–€7,733) in the year before DAA initiation and €8,193 (95% CI: €7,966–€8,442) in the fifth year after DAA initiation.

Compared to the general population, patients with chronic HCV infection treated with DAAs face a higher economic burden post-DAA therapy. The additional reimbursement expenditure associated with managing patients with chronic HCV infection compared with the matched general population was €5,781 (95% CI: €5,540–€6,028) in the fifth year after DAA therapy (Table 2). Except for medications, the amount reimbursed for managing patients with chronic HCV infection was similar on average in the years before and after DAA initiation (Table 2 and Supplementary Table 6).

DAA treatment uptake

The proportion of patients with chronic HCV infection treated with DAAs increased progressively after 2013 before reaching a quasi-plateau in 2019. By the end of 2021, the proportion of eligible patients with chronic HCV infection who received DAA treatment was 81.5% (Fig. 4).

Discussion

To the best of our knowledge, this study provides the first comprehensive assessment of the national economic burden of chronic HCV infection based on real-world data from French claims databases. It also evaluates the overall economic impact of DAA therapy at the national level. After analyzing data from more than 140,000 patients with chronic HCV infection over a 10-year period, three key findings emerged. First, the total reimbursement for managing patients with chronic HCV infection from 2012 to 2021 was approximately €12 billion. Second, by the end of 2021, the proportion of DAA treatment had reached 81.5% among eligible patients with chronic HCV infection in France. Third, even after receiving DAA therapy, patients with chronic HCV infection continue to bear a significant economic burden over the long term compared with the general population.

Several studies have investigated the economic burden of chronic HCV infection across different countries.¹²⁻¹⁵ A study based on Japanese nationwide administrative claims data explored healthcare expenditures among patients with HCV at different stages of the disease.¹⁴ The authors found that despite a 29% decrease in healthcare expenditures after HCV cure, the economic burden of chronic HCV infection remained high after DAA exposure. Notably, this study did not determine the total healthcare expenditures of patients with HCV. It only documented cases of healthcare expenditure for which HCV infection was recorded in claims databases, which may have underestimated the real economic burden of the disease and its related comorbidities. In France, a previous study quantified the economic burden of extrahepatic manifestations of chronic HCV infection.¹⁶ In two other French studies, economic data related to the burden of chronic HCV infection considered only hospital expenditures obtained from an analysis of the French National Hospital database.^{17,18} Contrastingly, our study aimed to explore the overall burden

associated with the clinical management of chronic HCV infection and related diseases through direct and indirect medical resource utilization. To our knowledge, no study has assessed the real-world economic burden of chronic HCV infection and its manifestations in the DAA era from a national health insurance perspective in France. Since healthcare coverage of chronic conditions is insured by the French national health insurance, previous economic results derived from commercially insured adults in other countries cannot be generalized to the French setting.¹⁹ To date, most of the evidence regarding the economic burden of HCV infection has relied on assumptions derived from the literature or expert opinion.¹⁶ By accessing the SNDS, we conducted a detailed analysis of claims databases using reliable reimbursement amounts. Notably, the use of the incremental costing method and the construction of a matched cohort from the general population without chronic HCV infection allowed us to determine the exact economic burden directly attributable to chronic HCV infection.²⁰ Compared with the matched general population without HCV infection, our findings revealed a persistent economic burden in patients with chronic HCV infection, even years after DAA therapy. This additional burden could be partly attributed to the specific profile of patients with chronic HCV infection, which often includes comorbidities associated with injection drug use and alcohol use disorders,^{21,22} as well as healthcare costs related to managing liver complications and extrahepatic manifestations of chronic HCV infection. Furthermore, our study revealed the limited impact of DAAs on the economic burden of hospital stay in patients with chronic HCV infection. Although the beneficial impact of DAAs on liver-related complications is well established, their extrahepatic impact is not fully understood.²³ Further research is needed to determine whether the causes of healthcare expenditure differ

before and after HCV treatment. Our results indicate that patients with chronic HCV infection remain at a higher risk of adverse clinical events, potentially leading to costly health management even after achieving a virological cure following DAA therapy. In a recent study analyzing 21,790 patients successfully treated for HCV with DAAs in British Columbia, Scotland, and England, the authors observed that the overall liver and drug-related mortality rates were significantly higher than those observed in the general population.²⁴ Consistently, our data suggest that the total burden of liver disease and general comorbidities associated with HCV infection cannot be fully mitigated with interferon-free antiviral regimens. Further research is essential to establish strategies that could mitigate the economic burden after HCV treatment. Policies aimed at reducing drug and alcohol misuse, along with enhanced surveillance and management of comorbidities in HCV patients, have the potential to significantly impact this burden positively. Additionally, the development of integrated care models that combine medical treatment for addiction with support services like mental health counseling, could lead to improved health outcomes and potentially reduce the economic burden following HCV treatment. Notably, our results do not support economic estimates based on the assumption that patients who have been virologically cured of HCV would exhibit health service utilization patterns similar to those without HCV infection.²⁵ Consequently, our results highlight the need for further comprehensive cost-effectiveness and cost-utility studies that accurately account for the persistent economic burden after HCV treatment, as revealed by the analysis of real-world data from claims databases.

A recent study, which compiled data from clinical trials and observational cohorts, estimated the proportion of patients with chronic HCV infection who received DAA treatment across several countries.²⁶ Nevertheless, because the authors derived the

proportion of patients who received DAA treatment from studies conducted in different years, this estimate may not accurately represent the current proportion of DAA treatment. In our study, we identified all DAAs at the national level among the national cohort of patients with chronic HCV infection. This approach allowed us to provide updated and robust estimates of the proportion of patients receiving DAA therapy in France. Importantly, the WHO has designated 2030 as the target year for achieving global HCV eradication, and France aims to eradicate HCV by 2025.⁸ Consequently, the significant proportion of patients not treated with DAA therapy supports reinforcing policies for universal access to DAAs.

Our study employed a previously validated algorithm to identify all patients with prevalent chronic HCV infection by analyzing nationwide claims databases until the end of 2021. The number of patients with chronic HCV infection identified in this study via the SNDS aligns with prevalence estimates from national surveys and studies that conducted blood sample analyses in the general population.^{27,28} It is important to note that our estimate of specificity was 85% and that we cannot totally exclude the possibility of classification error. Nevertheless, the algorithm was determined using HBV-infected patients as a control group and not using a representative sample of the HCV-negative population from the SNDS. Given that HBV- and HCV-infected patients had similar clinical characteristics and reimbursement data, the specificity of 85% should be considered very conservative. If this algorithm were applied to a representative sample of the SNDS, the risk of false positives and misclassifications would be much lower and the specificity would approach 100%.

The significant percentage of patients with chronic HCV infection still not being treated with DAAs by the end of 2021 highlights the need for future efforts to identify

better the social and structural barriers to care for this population. A previous study investigating the barriers to DAA initiation among patients with chronic HCV infection in the United States identified various factors, including fear of adverse events, belief in the need for alcohol abstinence before DAA initiation, and lower prioritization of chronic HCV infection compared to other illnesses.²⁹ In France, alcohol use disorders and the low density of HCV specialists at the regional level have been identified as factors delaying the initiation of DAAs in people who use drugs.^{30,31} Our study has several strengths. First, it used real-world data collected directly from French claims databases, which provide a precise assessment of the economic burden of chronic HCV infection and the impact of DAAs. The analysis assessing the impact of DAA therapy was highly robust, as it was based on economic observational data directly captured through the SNDS rather than external data not adapted to the French context. Second, the cohort of patients with chronic HCV infection was identified using a validated algorithm specifically developed to evaluate the public health burden of this disease.¹⁰ Third, the study investigated direct and indirect medical costs, including disability pensions, work-related accidents, occupational diseases, and transportation costs.

This study has two main limitations. First, we cannot entirely exclude the possibility of coding errors in the reimbursement data within the SNDS. Second, our results only captured the economic burden of chronic HCV infection from the French National Health Insurance perspective and did not include indirect nonmedical costs and out-of-pocket payments, including amounts reimbursed per additional health insurance. Thus, economic burden from a societal perspective could not be defined in this study.

In conclusion, this study is the first to assess the economic burden of chronic HCV infection from a national health insurance perspective. It revealed that a high economic burden persists in patients with chronic HCV infection even after DAA therapy. It is crucial to acknowledge the persistent economic burden caused by patients with chronic HCV infection, even after achieving HCV cure, and to establish specific interventions to alleviate this ongoing burden. The proportion of untreated patients at the national level underscores the need for reinforcing policies for universal access to DAAs. Further research is needed to evaluate the cost-effectiveness of DAA therapy using real-world data from the SNDS.

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Table 1. Economic Burden Attributable to Chronic Hepatitis C Virus Infection in France From 2012 to 2021 by Healthcare Sector

	Cumulative amount reimbursed (€)	Amount per patient per year (€)
Hospital pharmacy/expensive medications	4,411,875,444	4,145
Retail pharmacy	2,359,084,428	2,230
Hospital stays in public healthcare institutions	1,459,148,879	1,389
Disability pensions	443,901,796	420
Medical procedures/visits (outpatient hospital)	245,754,250	243
Medical devices (outpatient)	141,204,046	134
Transportation	138,759,271	129
Outpatient medical laboratory	130,164,901	126
Hospital stays in private healthcare institutions	129,680,410	122
Physician visits (outpatient)	120,155,466	118
Medical procedures (outpatient)	81,599,412	82
Work-related accident/occupational diseases	53,196,496	53
Total	9,714,524,799	9,191

Table 2. Reimbursement Attributable to the Management of Chronic Hepatitis C Virus Infection After Direct-acting Antiviral Therapy (per Patient per Year)

	Years relative to DAA treatment initiation					
	0	+ 1	+ 2	+ 3	+ 4	+ 5
Hospital pharmacy/expensive medications	€32,982	€5,554	€1,421	€1,170	€1,228	€1,300
Retail pharmacy	€7,944	€1,870	€1,434	€1,405	€1,447	€1,681
Hospital stays in public healthcare institutions	€1,846	€1,500	€1,348	€1,304	€1,171	€1,356
Disability pensions	€349	€395	€433	€462	€469	€539
Medical procedures/visits (outpatient hospital)	€425	€247	€182	€166	€163	€178
Medical devices (outpatient)	€134	€140	€136	€138	€143	€167
Transportation	€133	€121	€115	€112	€100	€112
Outpatient medical laboratory	€296	€154	€97	€88	€85	€97
Hospital stays in private healthcare institutions	€99	€92	€88	€95	€91	€95
Physician visits (outpatient)	€144	€120	€106	€99	€91	€92
Medical procedures (outpatient)	€103	€96	€94	€90	€91	€97
Work-related accidents/occupational diseases	€51	€49	€48	€48	€56	€67
Total	€44,505	€10,337	€5,502	€5,177	€5,134	€5,781

DAA, direct-acting antiviral.

Figure Legends:

Fig. 1. Flowchart of the Study

HCV, hepatitis C virus; SNDS, Système National des Données de Santé (French administrative health insurance databases)

Fig. 2. Evolution of Annual Reimbursements per Patient With Chronic Hepatitis C Virus Infection From 2012 to 2021 in France

This figure shows the trends in annual reimbursements per patient with chronic HCV infection in France from 2012 to 2021. The data are presented by the healthcare sector (e.g., hospitals and pharmacies), with each area representing a different sector. The y-axis represents the annual reimbursement per patient per year, whereas the x-axis represents the year.

Fig. 3. Annual Reimbursement Changes Before and After Direct-acting Antiviral Therapy in Patients With Chronic Hepatitis C Virus Infection

DAA, direct-acting antiviral

This figure shows the trends in annual reimbursements per patient treated with DAAs in the years preceding and following DAA therapy. The data are presented by the healthcare sector (e.g., hospitals and pharmacies), with each area representing a different sector. The y-axis represents the annual reimbursement per patient, whereas the x-axis represents the years relative to DAA treatment initiation.

Fig. 4. Proportion of Patients With Chronic Hepatitis C Virus Infection Who Received Direct-acting Antiviral Treatment From 2014 to 2021 in France

CHC, chronic hepatitis C; DAA, direct-acting antiviral; HCV, hepatitis C virus

The cumulative prevalence of chronic HCV infection eligible for DAA therapy (not treated or resolved with prior interferon/ribavirin treatment) is shown as a gray bar.

Patients previously treated with first-generation DAAs were excluded from the analysis.

145 187 patients with chronic HCV infection identified between 01/01/2010 and 12/31/2021

5 515 798 individuals without HCV infection sampled in the SNDS

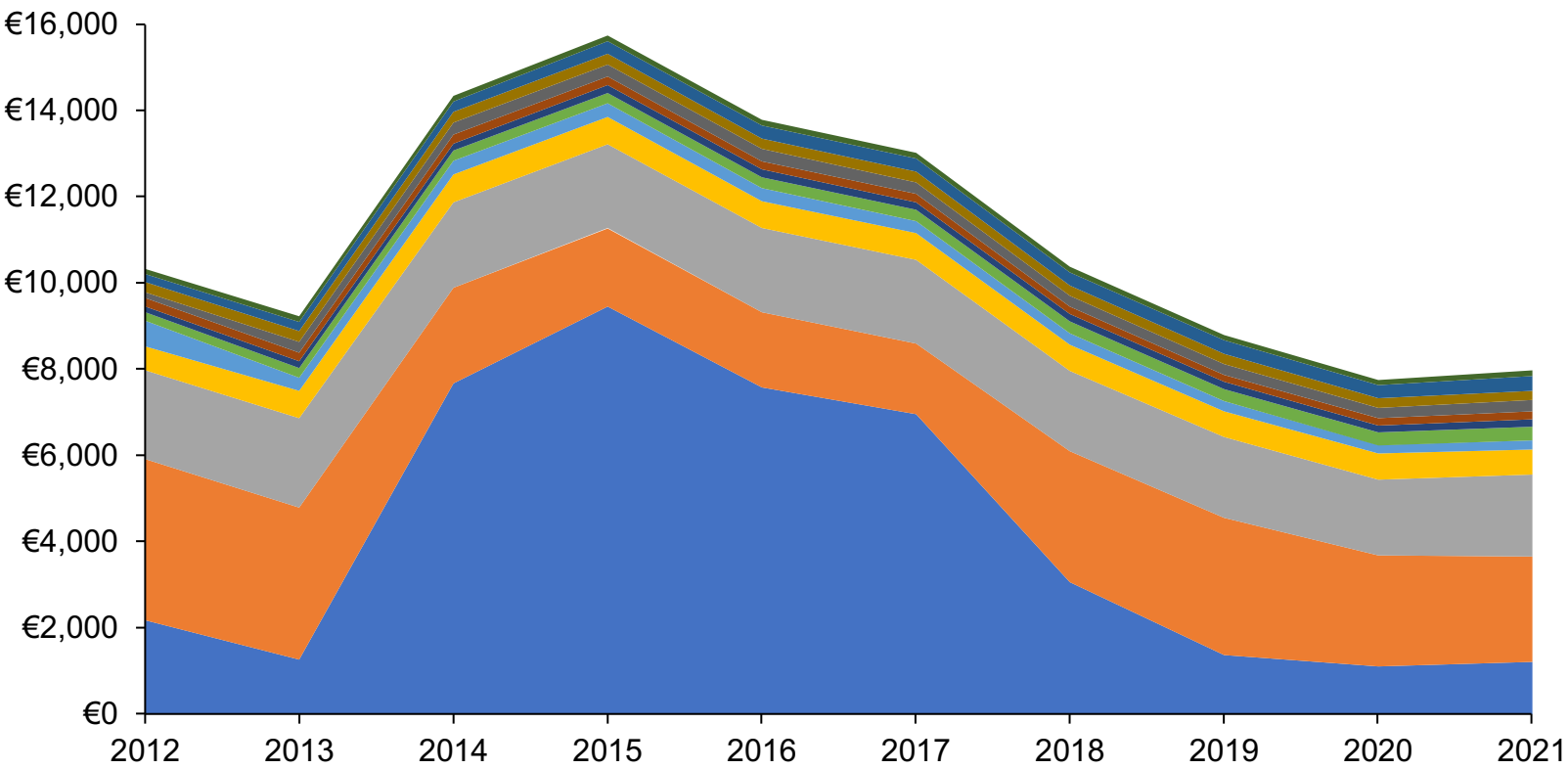
149 excluded:
- 149 birth date or death date miscoded or unknown

145 038 patients with chronic HCV infection eligible for the study

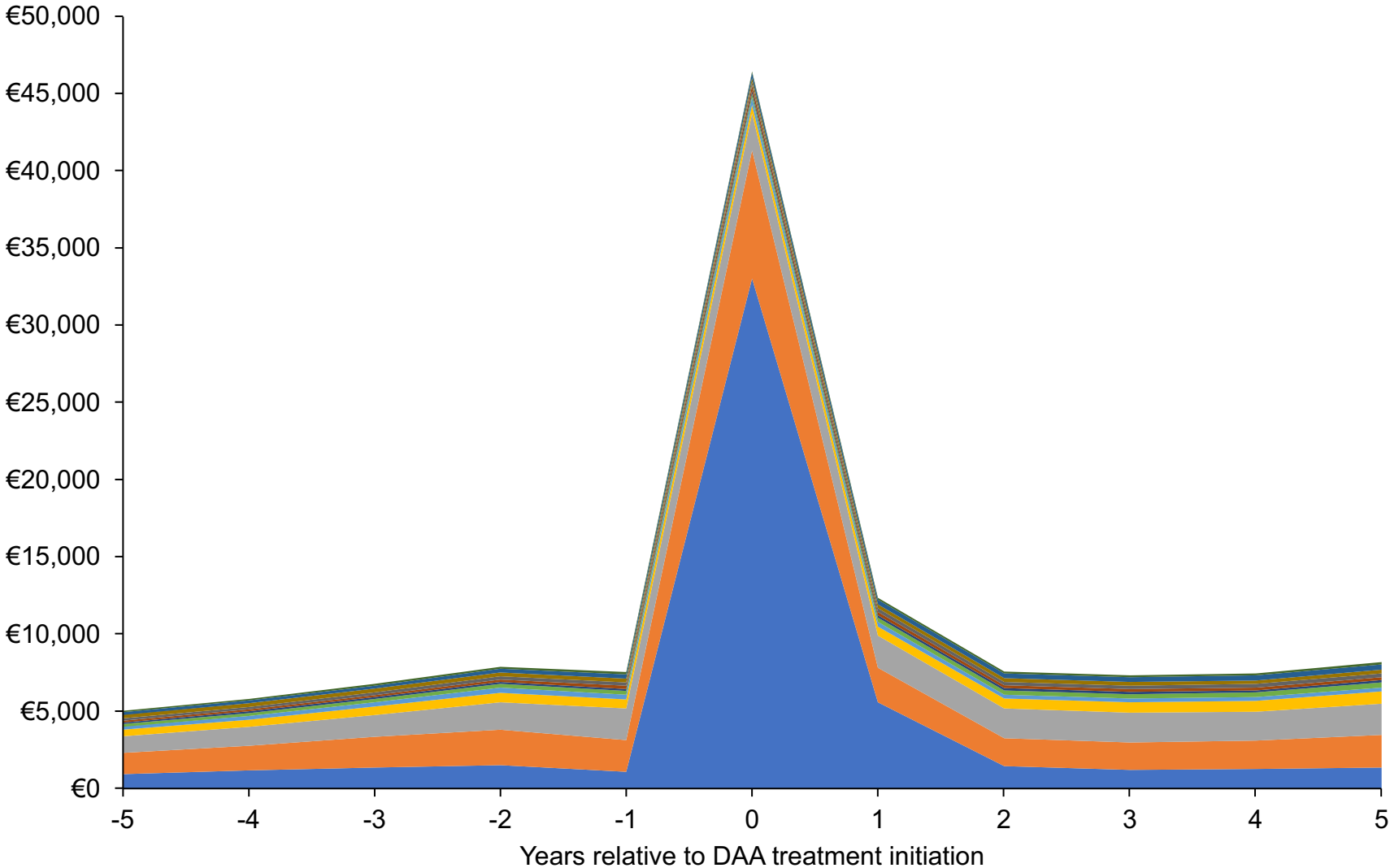
Matching 1:1 on birth date and sex of individuals aged 18 to 85 years

141 141 patients with chronic HCV infection

141 141 matched individuals from the general population



- Hospital pharmacy / expensive medications
- Retail pharmacy
- Hospital stays in public healthcare institutions
- Disability pensions
- Medical procedures / visits (outpatient hospital)
- Medical devices (outpatient)
- Transportation
- Outpatient medical laboratory
- Hospital stays in private healthcare institutions
- Physician visits (outpatient)
- Medical procedures (outpatient)
- Work-related accidents / occupational diseases



- Hospital pharmacy / expensive medications
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