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Public Health

journal homepage: www.elsevier.com/puhe

Original Research

New patterns emerge after a sustained increase in the incidence of hepatitis C virus infection from 2004 to 2017: a joinpoint regression analysis

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ARTICLE INFO

Article history:
Received 20 August 2018
Received in revised form
2 January 2019
Accepted 18 January 2019
Available online 28 March 2019

Keywords:
Hepatitis C
HCV
Incidence
Joinpoint
Trend

ABSTRACT

Objectives: Hepatitis C virus (HCV) infection continues to be a major public health concern in China. There is little information available in the literature about age- and sex-specific HCV incidence trends. The goal of this study was to examine recent trends in HCV incidence rates in Hunan, China, according to age and gender.

Study design: A descriptive study was implemented with a joinpoint analysis.

Methods: Based on the annual reported incidence data of hepatitis C in Hunan, China, from 2004 to 2017, we performed a joinpoint regression analysis to examine trends in the annual percentage change (APC) and the average annual percentage change (AAPC) in the incidence of HCV infection throughout the study period; we stratified the analysis by gender and age. The software calculates the APC, AAPC and the 95% confidence intervals for each trend segment and tests whether the slope for each segment has a significant difference from the prior segment using a Z test.

Results: From 2004 to 2017, the overall incidence rate of HCV infection rose from 0.93 per 100,000 to 20.88 per 100,000 (AAPC, 25.2%). In particular, women aged ≥65 years had the fastest increasing rate (AAPC, 29.9%). The incidence of different demographic groups showed no significant difference in increasing trends before 2013. However, new patterns emerged after 2013: the incidence of people aged 0–14 years was no longer significantly elevated; a significant yearly decline occurred in the incidence of HCV in people aged 15–29 years; the incidence of HCV in people aged ≥30 years continued to increase, with significantly slower increasing rates than before; and women aged ≥65 years showed a

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https://doi.org/10.1016/j.puhe.2019.01.014

significantly higher yearly increase in incidence than that in men in the same age group (APC, 11.1% in women versus 5.3% in men).

Conclusion: The overall increasing rate of HCV infection significantly slowed after 2007 and 2013. The differences in incidence trends among demographic groups have obviously increased in the last 5 years, and the reasons underlying these different trends urgently require further study. People in older age groups, especially women aged ≥65 years, still experienced increases in incidence rates in the last 5 years. This finding indicates that programmes for the prevention and control of HCV infection in older people require continued strengthening.

Introduction

Hepatitis C virus (HCV) is transmitted through exposure to infectious blood or fluids and is characterized by persistent infection and chronicity. HCV infection is recognized as a major cause of chronic liver disease worldwide. According to statistics from the World Health Organization, an estimated 71 million people have chronic HCV infections worldwide. It is estimated that approximately 399,000 people worldwide die of HCV-related liver disease each year.[1,2] HCV is the only viral hepatitis infection associated with increasing age-specific disability-adjusted life year rates.[3] HCV infection has been an international public threat for almost all countries, especially Africa and Asia.[4] Most previous studies generally showed that men were more vulnerable to HCV infection than women, but other studies on intravenous drug use have suggested a significantly higher incidence among women than men.[5–7]

The incidence of viral hepatitis in China is dominated by hepatitis B virus (HBV) and HCV infections, accounting for 80.90% and 9.25% of the total reported cases of viral hepatitis, respectively.[8] China introduced HBV vaccination into the child immunization programme in 2002, and the number of acute HBV infection cases in Chinese adults and children has decreased significantly in recent years. In contrast, HCV infection remains serious in some parts of China.[9–11] Owing to the lack of a long-term effective vaccine for HCV prevention, progress in HCV treatment has been especially important. The advent of direct antiviral agent (DAA) therapy provides a highly efficacious treatment regimen for patients with chronic HCV; nevertheless, the unavailability in some areas, insufficiency of optimal medical evidence in special patients and high cost will be great challenges.[12,13]

The joinpoint regression method shows some advantages in trend analysis.[14] The incidence trend will be divided into several statistically significant segments by fitting the joinpoint model, and this kind of segmentation based on statistical processing is more scientific and reasonable than subjective segmentation. There are few joinpoint regression analyses for infectious diseases in China. A national study in 2017 analyzed the trends in the incidence of 45 notifiable infectious diseases in China using joinpoint regression analysis, and the results indicated that HCV infection was one of the diseases that had the fastest growth in incidence among Chinese people; however, studies of incidence trends in different age and gender groups were not conducted.[15] Hunan, a province of China, is located in central southern China. There is little information available on age- and sex-specific HCV incidence trends. Therefore, in the present study, the objective was to use the joinpoint model to provide information on the incidence trends of HCV infection and the correlation with different ages and genders in Hunan from 2004 to 2017.

Methods

Data collection

A routine reporting system for selected infectious diseases was established in China in the 1950s.[16] In 2003, the China Information System for Diseases Control and Prevention was established as a Web-based routine reporting system operating through administrative grading responsibility and territorial management.[17] This system includes incidence rates, mortality data and population counts for all provinces in mainland China by gender, age, year and place of residence.

At the end of 2017, the urbanization rate of Hunan Province was 54.62%, and Hunan is a major agricultural province. The overall economic level of Hunan is intermediate in China. In recent years, the high-tech industry has become a new growth point for the economy of Hunan. In terms of health care, the quality of infectious disease reports in Hunan has always been at the forefront of China. We obtained population counts and annual HCV incidence cases (registered by onset dates) for all individuals in Hunan between 2004 and 2017 from the China Information System for Diseases Control and Prevention. According to the results of the joinpoint regression analysis on age-specific incidence rates, we stratified the analysis by age (in years: 0–14; 15–29; 30–64; 65~) and gender. Age standardization was based on the 2010 China Census data and performed using the direct method.

Statistical analysis

First, we used Excel to extract, sort and clean the data. We defined incidence (per 100,000) as the number of incident cases divided by the population scale. Then, we performed joinpoint regression modelling using Joinpoint software, version 4.5, (US National Cancer Institute) to examine the trends in the annual percentage change (APC) and average annual percentage change (AAPC) in the incidence of HCV infection throughout the study period.[14] The Monte Carlo permutation test is used to give the numbers, positions and corresponding *P*-values of the joinpoints (with an overall significance level of 0.05); this method has been widely used to analyze trends in incidence rates.[18] The null hypothesis was tested using a maximum number of 2 joinpoints in the analysis on time trends but a maximum number of 3 joinpoints in the analysis on age-specific rates. The software calculates the APC and AAPC and their 95% confidence intervals for each trend segment and tests whether the slope for each segment has a significant difference from the prior segment using a *Z* test. In describing trends, we used the terms increase or decrease if the slope was significant ($P < 0.05$). We used the term stable to represent the non-significant slope ($P \geq 0.05$).

Results

The age was divided into 4 segments by model fitting. People aged 0–14 years showed a relatively low incidence of HCV infection. The incidence showed an increasing trend with increasing age in the 15- to 29- and 30- to 64-year-old age groups. The incidence of HCV infection in people aged ≥65 years was high. The pairwise comparison by the Joinpoint software showed that the age-specific incidence rates were not parallel between males and females ($P = 0.008$), and a significant difference was observed in the 15- to 34-year old age groups and in those aged ≥65 years (Table 1). According to this analysis, the time trend of incidence was evaluated in 4 age groups: 0 to 14, 15 to 29, 30 to 64, and ≥65 years.

In the entire period from 2004 to 2017, the overall incidence rate of HCV infection rose from 0.93 per 100,000 to 20.88 per 100,000 (AAPC, 25.2%). The overall incidence rate increased in a similar fashion in men and women, from 1.29 per 100,000 to 20.94 per 100,000 in men (AAPC, 24.1%) and from 0.86 per 100,000 to 19.14 per 100,000 in women (AAPC, 25.1%). The incidence of HCV infection showed a significant increase in all age groups from 2004 to 2017. In particular, women aged ≥65 years had the fastest increasing rate (AAPC, 29.9%). People aged <30 years had a significantly lower yearly increase in incidence than people aged 30–64 years (AAPC, 12.1–13.1% versus 26.2%). People aged 15–29 years had a significantly lower yearly increase in incidence than people aged ≥65 years (AAPC, 13.1% versus 26.1%) (Fig. 1, Fig. 2, Table 2). However, the AAPC obscured some important differences by age and gender.

The incidence trend of HCV infection in the whole population was divided into 3 periods by joinpoint model fitting, and the significant changes occurred in 2007 and 2013; the yearly increase in the later periods was significantly lower than that in the previous periods (APC, 2.5% versus 26.4% versus 60.3%). People aged 0–14 years showed a significant increase in incidence before 2012 (APC, 24.8%) and a stable trend after 2012 (APC, −5.5%). People aged 15–29 years first showed an increasing trend before 2007 (APC, 57.7%), then, the increasing rate slowed (APC, 14.5%) and in the last period, a significant yearly decline occurred (APC, −13.6%). The incidence of HCV infection continuously rose during the whole study period among people aged ≥30 years, with increasing rates slowing gradually. Nevertheless, the increasing trend after 2013 among people aged ≥65 years was mainly observed in women, and women aged ≥65 years showed a significantly higher yearly increase in incidence than men in the same age group (APC, 11.1% in women versus 5.3% in men) (Table 3).

Discussion

In the present joinpoint regression analysis, we quantified the incidence trends of HCV infection between 2004 and 2017 in Hunan. Although the overall yearly incidence of HCV infection showed an increasing trend from 2004 to 2017, this increase significantly slowed after 2007 and 2013. In the past, unsafe injection was the most common cause of HCV infection in developing countries. However, owing to medical improvement measures and changeable human behaviours in recent decades, the main risk factors for HCV infection have changed and intravenous drug use and high-risk sexual behaviour have gradually played important roles in HCV infection.[19–21] In addition, in the past few years, several factors could also account for the increasing trend. First, the diagnostic levels for HCV infection have improved gradually in recent years. In particular, sensitive serology tests and real-time quantitative polymerase chain reaction technologies have become widespread. Moreover, the timeliness of infectious disease reporting has meliorated. Second, the connectivity of humans

Table 1 – Joinpoint regression analysis on the age-specific incidence of HCV infection in Hunan, China.[a]

Sex	Segment 1 (slope)	Segment 2 (slope)	Segment 3 (slope)	Segment 4 (slope)
Both	0–14 (−0.189)	15–29 (0.224^)	30–64 (0.025^)	65~ (−0.016)
Male	0–14 (−0.130)	15–34 (0.156^)	35~ (0.010^)	
Female	0–14 (−0.161)	15–29 (0.200)	30–64 (0.031^)	65~ (−0.037)

HCV: hepatitis C virus.

[a] Age interval; ^: $P < 0.05$. For males, segment 1 is the age interval with stable incidence, segment 2 is the age interval with a rapid increase in incidence and segment 3 is the age interval with a slow increase in incidence. For females, only segment 3 is the age interval with rising incidence, whereas the other segments are the age intervals with stable incidence.

has gradually increased. The farmer patients accounted for the highest proportion (up to 50%) of the total reported cases of HCV infection in Hunan. Evidence suggests that more than 10% of the population in China has moved from rural areas to city centres for better economic sources, which may promote the spread of infectious diseases.[16,22]

We found that the increase in the incidence of HCV infection in the past 5 years was all among the middle-aged and elderly populations, especially in people aged ≥65 years. Liu et al.[23] used empirical mode decomposition to describe the incidence trend of HCV from 2004 to 2014 and found that HCV is much more prevalent among older people in China. This prevalence could be a cumulative effect of exposure to HCV transmission risks over a lifetime. HCV infection is occult and progresses slowly; thus, most patients are asymptomatic or have only mild symptoms after infection in young age and are not diagnosed until after middle age. A Chinese study indicated that people born between 1960 and 1980 had the highest risk of HCV infection, and this birth cohort might have specific exposure to HCV.[24] Moreover, a national study in China indicated that the number and composition ratio of high-age human immunodeficiency virus (HIV)/AIDS cases that were transmitted through heterosexual sex pathways increased annually.[25] HCV has the same route of transmission as HIV. Therefore, HIV merging with HCV infection is common. Among the global HIV-infected persons, those infected with HCV account for 20–30% of HIV-infected persons, whereas the rate of coinfection of HCV was as high as 61.29% in Hunan.[26,27] With the increase of population ageing, the high incidence of HCV infection among elderly people will bring a great threat to Chinese public health.

In contrast, with middle-aged and elderly people, there have been some favourable trends in young individuals (<30 years) since 2012 (or 2013), especially people aged 15–29 years. The decline in the incidence of HCV infection in young people may be attributable to several factors, such as the enhancement of blood safety management, widespread use of disposable syringes and the spread of knowledge about blood-borne diseases, such as AIDS.[28] In addition, DAA therapy, a new effective treatment regimen, has been shown to have a cure rate of more than 90% for chronic HCV infection in existing studies. Moreover, with the increasingly serious HCV epidemic, the Chinese government has incorporated HCV control into the AIDS prevention and control network to provide reliable monitoring support for the prevention and control of HCV infection.

To our knowledge, this study describes for the first time the trends of age- and sex-specific incidence rates in HCV infection in China using the joinpoint regression method. Although most studies have described the epidemiology of HCV among the general population, a lack of information on age- and sex-specific differences is the norm.[29–31]

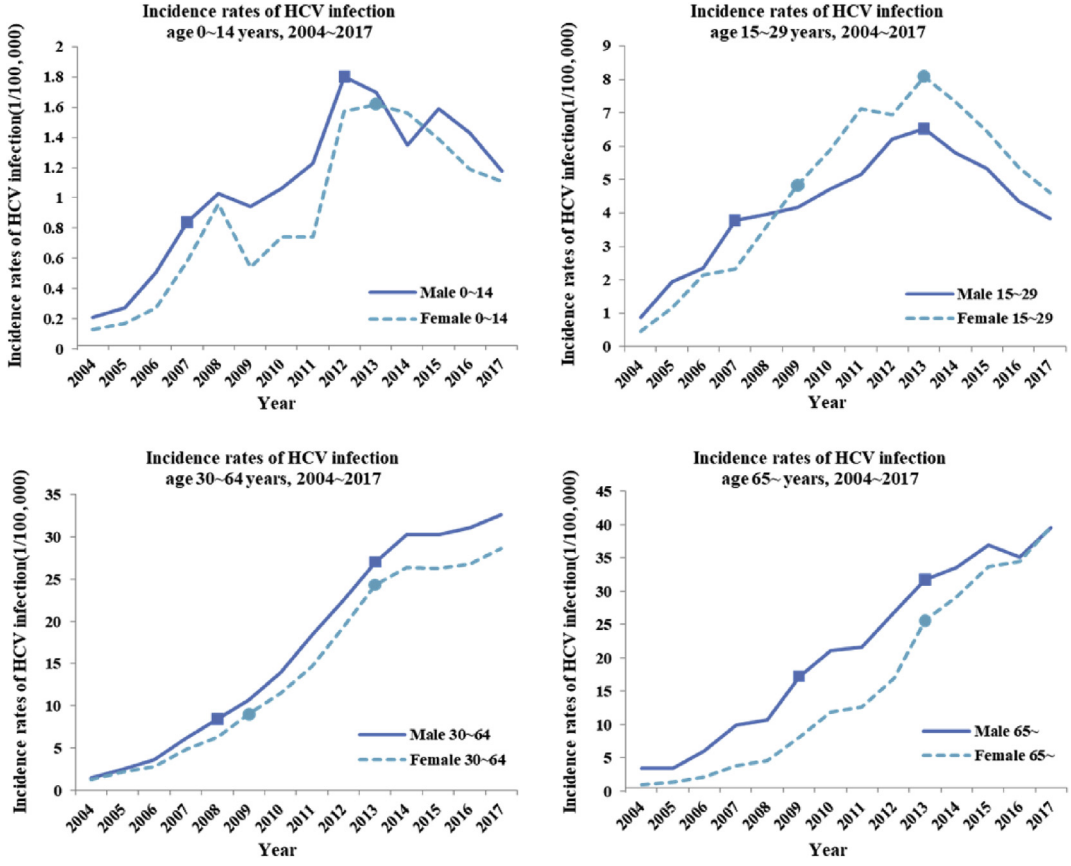

Fig. 1 – Incidence trends of HCV infection in age groups of 0–14, 15 to 29, 30 to 64 and ≥65 years in Hunan, China, from 2004 to 2017. The locations of the marking points on the line graphs are the same as those of the joinpoints on the joinpoint regression curves. HCV: hepatitis C virus.

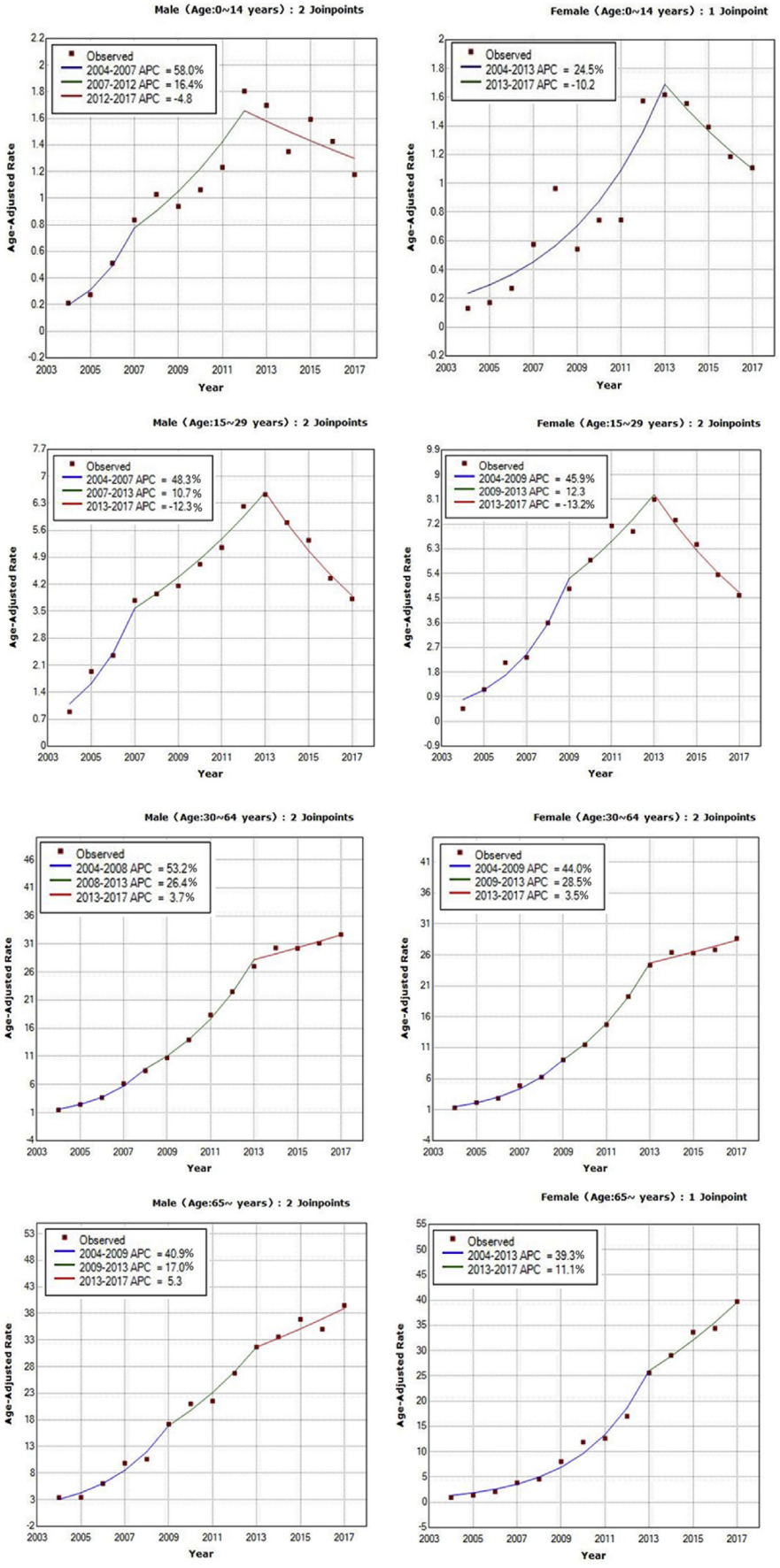

Fig. 2 – Joinpoint regression analysis of the age-adjusted rate of HCV infection in Hunan, China, by gender and age, from 2004 to 2017. APC: annual percentage change; HCV: hepatitis C virus.

Table 2 – AAPC in incidence of HCV infection, by gender and age, 2004 to 2017.

Age group (years)	AAPC	95% CI	HCV infections, n	Individuals at risk, n
0–14 y				
Male	15.6%	7.0 to 25.0	1009	88,547,202
Female	12.6%	2.7 to 23.4	721	76,718,495
Total	12.1%	4.6 to 20.2	1730	165,265,697
15–29 y				
Male	10.2%	5.1 to 15.6	4676	110,860,451
Female	14.7%	7.5 to 22.4	5138	104,794,722
Total	13.1%	8.8 to 17.4	9814	215,655,173
30–64 y				
Male	26.2%	23.9 to 28.5	40,187	231,416,304
Female	25.6%	22.4 to 29.0	33,077	219,396,360
Total	26.2%	23.9 to 28.5	73,264	450,812,664
65~ y				
Male	21.7%	14.9 to 28.8	9406	41,532,897
Female	29.9%	25.1 to 35.0	7440	42,880,979
Total	26.1%	19.0 to 33.7	16,846	84,413,876
All age groups				
Male	24.1%	22.2 to 26.1	55,278	472,356,854
Female	25.1%	22.2 to 28.0	46,376	443,790,556
Total	25.2%	22.4 to 28.1	101,654	916,147,410

AAPC: average annual percentage; CI: confidence interval; HCV: hepatitis c virus; $P < 0.05$.

Both the time trend analysis and age-specific rate analysis in our study showed differences in HCV infections with regards to gender. In our study, the incidence of HCV infection in men was significantly higher than that in women, which was consistent with other studies.[32,33] However, some unfavourable trends in women were found in the present study. In the last 5 years, the observed increasing trend reflects mainly an increase in incidence among women aged ≥65 years (APC, 11.1%). Furthermore, women aged ≥65 years showed a significantly higher yearly increase in incidence than men in the same age group in recent years, in contrast with the higher spontaneous clearance rate of HCV among women.[34] A study in Canada indicated that differences in male and female rates of HCV infection have narrowed since 2005.[31] Although the causes of a higher increase in incidence among elderly women in the last 5 years are unclear, there are some possible supportive points. First, women are more likely to contact or enter the healthcare system and be tested than men.[35,36] Resident health files are established when medical and health institutions provide medical and health services to residents. A study in Hunan reported a higher creation rate of resident health files among women than men and among people aged ≥65 years than people in other age groups.[37] Second, although there are some conflicting reports, several studies on intravenous drug users have shown a higher incidence of HCV infection in women than that in men.[38] In the past two decades, intravenous drug use has gradually become an important risk factor for HCV infection. Notably, the incidence of HCV infection among women aged 15–29 years was higher than that among men in the same age group after 2009, which revealed that more women are at the risk of HCV infection, and the cumulative effect of exposure to risk factors for HCV infection may also lead to more cases in older women in the future. In addition, oestrogen plays an important role in the spontaneous clearance of HCV; hence, oestrogen reduction and genetic variations in the oestrogen receptor gene might contribute to increased susceptibility in women.[39,40]

One important limitation of our study is the possible misclassification of chronic HCV infection as acute. Owing to the lack of specific markers for acute HCV infection, the serological data can often overestimate the number of patients with active chronic infection. Some factors, such as differences in diagnostic criteria, experimental conditions and technical levels in different medical institutions, could affect incidence reporting. The trend analysis cannot explain the

Table 3 – APC in incidence of HCV infection, by gender and age, 2004 to 2017.

Age group (years)	Period 1		Period 2		Period 3	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
All population	2004–2007	60.3% (43.1–79.7)	2007–2013	26.4% (23.8–29.0)	2013–2017	2.5% (0.6–4.5)
0–14 y						
Male	2004–2007	58.0% (11.1–124.7)	2007–2012	16.4% (3.3–31.2)	2012–2017	−4.8% (−11.3 to 2.3)
Female	2004–2013	24.5% (11.1–39.4)	2013–2017	−10.2% (−28.7 to 13.3)		
Total	2004–2012	24.8% (12.2–38.8)	2012–2017	−5.5% (−16.4 to 6.7)		
15–29 y						
Male	2004–2007	48.3% (19.6–83.9)	2007–2013	10.7% (5.2–16.5)	2013–2017	−12.3% (−18.5 to −5.6)
Female	2004–2009	45.9% (25.3–69.8)	2009–2013	12.3% (−3.6 to 30.8)	2013–2017	−13.2% (−21.4 to −4.1)
Total	2004–2007	57.7% (32.0–88.4)	2007–2013	14.5% (10.2–19.0)	2013–2017	−13.6% (−17.9 to −8.9)
30–64 y						
Male	2004–2008	53.2% (43.9–63.1)	2008–2013	26.4% (23.1–29.7)	2013–2017	3.7% (1.9–5.6)
Female	2004–2009	44.0% (34.7–53.9)	2009–2013	28.5% (21.0–36.6)	2013–2017	3.5% (0.7–6.4)
Total	2004–2008	51.3% (42.1–61.1)	2008–2013	27.9% (24.6–31.2)	2013–2017	3.5% (1.7–5.4)
65~ y						
Male	2004–2009	40.9% (21.9–62.9)	2009–2013	17.0% (2.4–33.6)	2013–2017	5.3% (−0.7 to 11.7)
Female	2004–2013	39.3% (31.5–47.6)	2013–2017	11.1% (4.5–18.1)		
Total	2004–2009	44.1% (23.9–67.6)	2009–2013	23.9% (8.8–41.2)	2013–2017	8.7% (3.0–14.7)

APC: annual percentage change; CI: confidence interval; HCV: hepatitis C virus; $P < 0.05$.
Periods 1, 2 and 3 are time intervals determined by joinpoint analysis.

direct causes of the increase or decrease in the incidence rates, and the reasons underlying these different trends require further study. Although our study has limitations, a detailed historical comparison of incidence rates of HCV infection was conducted. In addition, the joinpoint regression analysis provides an unbiased estimate of significant changes in incidence trends over time.

Conclusions

The overall yearly incidence of HCV infection showed an increasing trend from 2004 to 2017. However, this overall increasing rate significantly slowed after 2007 and 2013, which indicates that the HCV preventive measures and the new anti-HCV treatment have played a certain effective role in reducing the population disease burden. The differences in incidence trends among demographic groups have obviously increased in the last 5 years, and the reasons underlying these different trends urgently require further study. The incidence rates of HCV infection in the low-age groups have declined steeply or have been stable since 2013. However, people in high-age groups, especially women aged ≥65 years, still experienced increases in incidence rates in the last 5 years. This finding indicates that programmes for the prevention and control of HCV infection in older people require continued strengthening, and the detection of HCV in women should not be overlooked in the future. The early detection of HCV infection in a high-age population is of great significance; on the one hand, early detection can reduce second-generation transmission, and on the other hand, early antiviral therapy can reduce liver damage, prevent disease progression and improve the quality of life of patients. In addition, precautions in medical settings, health campaigns for drug abusers and sexual educational campaigns are the most powerful control measures essential to reduce the prevalence of HCV infection.

Author statements

Acknowledgements

The authors thank everyone working for this study. The authors also thank the relevant departments for providing research data.

Ethical approval

No ethical approval was required or sought for the study because there was no interaction or intervention with human participants.

Funding

No funding source to declare.

Competing interests

Authors declare there is no conflict of interest.

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