Global burden of atherosclerotic cardiovascular disease in people with hepatitis C virus infection: a systematic review, meta-analysis, and modelling study

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Summary

Background

More than 70 million people worldwide are estimated to have hepatitis C virus (HCV) infection. Emerging evidence indicates an association between HCV and atherosclerotic cardiovascular disease. We aimed to determine the association between HCV and cardiovascular disease, and estimate the national, regional, and global burden of cardiovascular disease attributable to HCV.

Methods

For this systematic review and meta-analysis, we searched MEDLINE, Embase, Ovid Global Health, and Web of Science databases from inception to May 9, 2018, without language restrictions, for longitudinal studies that evaluated the risk ratio (RR) of cardiovascular disease in people with HCV compared with those without HCV. Two investigators independently reviewed and extracted data from published reports. The main outcome was cardiovascular disease, defined as hospital admission with, or mortality from, acute myocardial infarction or stroke. We calculated the pooled RR of cardiovascular disease associated with HCV using a random-effects model. Additionally, we calculated the population attributable fraction and disability-adjusted life-years (DALYs) from HCV-associated cardiovascular disease at the national, regional, and global level. We also used age-stratified and sex-stratified HCV prevalence estimates and cardiovascular DALYs for 100 countries to estimate country-level burden associated with HCV. This study is registered with PROSPERO, number CRD42018091857.

Findings

Our search identified 16 639 records, of which 36 studies were included for analysis, including 341739 people with HCV. The pooled RR for cardiovascular disease was 1·28 (95% CI 1·18–1·39). Globally, 1·5 million (95% CI 0·9–2·1) DALYs per year were lost due to HCV-associated cardiovascular disease. Low-income and middle-income countries had the highest disease burden with south Asian, eastern European, north African, and Middle Eastern regions accounting for two-thirds of all HCV-associated cardiovascular DALYs.

Interpretation

HCV infection is associated with an increased risk of cardiovascular disease. The global burden of cardiovascular disease associated with HCV infection was responsible for 1·5 million DALYs, with the highest burden in low-income and middle-income countries.

Funding

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Introduction

Globally, more than 70 million people are estimated to have hepatitis C virus (HCV) infection.1 Prevalence of HCV is particularly high in the eastern Mediterranean region and Europe, where approximately 2·3% and 1·5% of the general population have HCV infection, respectively.1 In the USA, the estimated prevalence of past or current HCV infection is 1·4%, affecting 4·6 million people, of whom at least 3·5 million have active HCV infection (1% of the general population).3 The number of new infection cases of HCV infections in the USA has been increasing since 2010.4 After acute HCV infection, most patients develop chronic infection.5 Usually, these patients remain asymptomatic, with less than a third progressing to liver cirrhosis in the subsequent 20–30 years.4 Although mortality due to cirrhosis and hepatocellular carcinoma are well recognised long-term complications of chronic HCV infection,4,14 patients with chronic infection are also at increased risk of non-liver-related mortality, including cancer and cirrhotic death.7

Atherosclerotic cardiovascular disease is the most common cause of death worldwide and the burden of disease is projected to rise substantially over the next few decades, particularly in low-income and middle-income countries (LMICs).15 HCV transmission is also projected to rise considerably in LMICs due to unsafe health-care practices and injection drug use.16–18 Published data19–24 suggest that the long period of chronic HCV infection might lead to the development of atherosclerotic...
Research in context

Evidence before this study
We searched PubMed from database inception to Jan 1, 2018, for systematic reviews and meta-analyses evaluating the association between hepatitis C virus (HCV) infection and atherosclerotic cardiovascular disease using the search terms “myocardial infarction”, “stroke”, “cerebrovascular disease”, “cardiovascular disease”, and “hepatitis C”. We found no studies that assessed the risk of cardiovascular disease or calculated the burden from all major atherosclerotic cardiovascular events associated with hepatitis C. Previous meta-analyses have evaluated the association between HCV infection and stroke and surrogate markers of subclinical atherosclerotic disease.

Added value of this study
To our knowledge, our study is the first meta-analysis to investigate the risk of major atherosclerotic cardiovascular disease in people with HCV infection and to estimate the burden of atherosclerotic cardiovascular disease attributed to HCV infection at the global, regional, and national level.

Implication of all the available evidence
Our findings show that people with HCV infection have a higher risk of cardiovascular disease than those without. The global burden of cardiovascular disease attributable to HCV accounted for a substantial number of disability-adjusted life-years in 2015, and the majority of the burden was borne by low-income and middle-income countries. These finding highlights the importance of public health strategies to eradicate HCV infection to reduce the burden of not only hepatic, but extrahepatic complications (such as cardiovascular disease), especially in regions with high HCV prevalence.

cardiovascular disease because of derangements in metabolic pathways and chronic inflammation. However, the direction and strength of the association between HCV infection and cardiovascular disease remains uncertain.15–19

Our study aimed to determine the association between HCV infection and the risk of cardiovascular disease to establish the global burden of cardiovascular disease attributable to HCV.

Methods
Search strategy and selection criteria
We searched MEDLINE, EMBASE, Ovid Global Health, and Web of Science from database inception to May 9, 2018, for original peer-reviewed articles using the search terms “myocardial infarction”, “stroke”, “cerebrovascular disease”, “cardiovascular disease”, and “hepatitis C” with no language restrictions. Full search terms are in the appendix (pp 2, 3). Additionally, we manually searched relevant review articles and bibliographic reference lists of studies selected for inclusion in our meta-analysis.

We included all longitudinal studies (case-control studies, cohort studies, and randomised controlled trials) that reported risk ratios (RRs) for hospital admission due to atherosclerotic cardiovascular disease or cardiovascular mortality in people with HCV compared with people without HCV. When there were multiple publications using data from the same cohort, we selected the article that reported the longest follow-up period. Detailed full-text review and data extraction was done independently by at least two investigators (KKL, DS, RB, or MA) and any disagreements were resolved by a third investigator (ASVS). We contacted authors for additional data or clarification if required. This study was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (appendix pp 4, 5).20 The study protocol is available online.

For studies that stratified the study population according to the presence of HCV RNA viraemia, we used the RR estimates pertaining to individuals who were HCV RNA positive. We defined a cardiovascular event as hospital admission with, or mortality from, acute myocardial infarction or stroke. Studies that evaluated a composite of acute cardiovascular events that included myocardial infarction or stroke but were not exclusive to these conditions were also included. For studies that stratified stroke events into haemorrhagic and ischaemic strokes, we included only ischaemic strokes in the analysis because haemorrhagic strokes have distinct pathophysiological mechanisms that are unrelated to atherosclerosis.21

Data analysis
We extracted RR estimates comparing cardiovascular events in people with HCV versus those without HCV from published reports using a standardised data extraction sheet. We estimated pooled RRs with 95% CIs. Since this outcome was relatively uncommon, we pooled studies that reported odds ratio and RR. We also assumed independence between risk estimates for different endpoints reported within studies, consistent with our previous analysis.22 We did a subgroup analysis stratified by outcome, HIV co-infection, publication year, risk of bias, definition of outcome event, and geographical location.

Two independent investigators (KKL and DS) assessed individual studies for risk of bias, using the degree of adjustment for confounders as the primary domain, and any disagreements were adjudicated by a third investigator. Studies that had adjusted for age, sex, and at least one other confounder were classified as being at low risk of bias. Studies that adjusted for fewer confounders than this were classified as moderate or high risk: studies that adjusted for either age or sex without any other confounders were classified as moderate risk of bias and...
those that did not adjust for both age or sex were classified as high risk of bias. We did the subgroup analysis stratified by risk of bias.

We estimated the burden of cardiovascular disease attributable to HCV at the national, regional, and global level. We obtained 2015 global prevalence estimates of viraemic HCV (HCV RNA positive) for 100 countries from the Polaris Observatory, with estimates stratified by Global Burden of Disease region. These 100 countries represent more than 85% of the global population and where more than 89% of all HCV viral infections (HCV RNA positive) are estimated to occur worldwide. The national prevalence estimates obtained were age-specific and sex-specific. We obtained age-specific and sex-specific disability-adjusted life-year (DALY) estimates for cardiovascular disease (DALYs due to ischaemic heart disease and stroke) for all adults aged older than 20 years in 2015 from the Institute of Health Metrics and Evaluation. The national prevalence estimates obtained were age-specific and sex-specific. We obtained age-specific and sex-specific disability-adjusted life-year (DALY) estimates for cardiovascular disease (DALYs due to ischaemic heart disease and stroke) for all adults aged older than 20 years in 2015 from the Institute of Health Metrics and Evaluation.

We then used national, regional, and global level attributable fractions to calculate the burden as previously described (appendix pp 6–10):

\[
\text{DALYs attributable to HCV} = \text{Cardiovascular DALYs} \times \text{PAF}
\]

For the extraction databases, data used to derive pooled estimates, burden estimates, and R code script see https://github.com/kk-lee/hcv

Figure 1: Study selection

For more on the Polaris Observatory see http://polarisobservatory.org/
| Cohort name          | Country or region | Study type                      | Data source                                                                 | Participants, n | Events, n | Men, n (%) | Mean age at baseline, years | Study period | Hepatitis C virus status | Outcome definition                  |
|----------------------|-------------------|---------------------------------|------------------------------------------------------------------------------|-----------------|-----------|------------|----------------------------|--------------|-------------------------|-------------------------------------|
| Heo et al, 2018      | USA               | Cohort study                    | Organ Procurement and Transplant Network                                     | 2728            | 117      | 1996 (73%) | 50.9                       | 2004-14      | Seropositive             | Cardiovascular disease              |
| Alvaro-Meca et al, 2014 | Spain             | Case-control study              | Spanish Minimum Basic Data Set                                               | 4091            | 369      | 3248 (79%) | 45                         | 1997-2013    | Seropositive             | Stroke†                             |
| Butt et al, 2017     | ERCHIVES, USA     | Cohort study                    | Veterans Health Administration                                               | 171,726        | 5949     | 171,726 (100%) | 54                        | 2001-15      | Viraemic                | Myocardial infarction              |
| Tripathi et al, 2017 | USA               | Cohort study                    | Veterans Health Administration                                               | 168,256        | 11,753   | 168,256 (100%) | 55                        | 2001-14      | Seropositive             | Cardiovascular disease              |
| Goodkin et al, 2017  | DOPPS, Multiple†  | Cohort study                    | Hospital records                                                             | 76,689         | 6,790    | 46,016 (59%) | 62.5                       | 1996-2015    | Seropositive             | Cardiovascular disease, myocardial infarction, stroke |
| Kovari et al, 2017   | Switzerland       | Cohort study                    | Swiss HIV Cohort Study                                                       | 5006            | 143      | 3624 (72%)  | 50                         | 1994-2014    | Seropositive             | Cardiovascular disease†             |
| Piazza et al, 2016   | USA               | Cohort study                    | Hospital records                                                             | 143             | 19       | 101 (71%)  | 55                         | 2005-10      | Undefined               | Cardiovascular disease              |
| Fernandez-Montero et al, 2015 | Spain | Cohort study | Hospital register                                                              | 1066           | 29       | 842 (79%)  | 42.7                       | 2004-15      | Viraemic                | Cardiovascular disease†             |
| Tsai et al, 2015     | NHIRD-HCV, Taiwan | Cohort study                    | National Health Insurance Research Database                                 | 69,915         | 848      | 35,936 (51%) | 54.7                       | 1998-2008    | Undefined               | Myocardial infarction               |
| Vajdic et al, 2015   | Australia         | Cohort study                    | Pharmaceutical Drugs of Addiction System                                    | 29,571         | 122      | 20,403 (69%) | 26                        | 1993-2007    | Seropositive             | Cardiovascular disease†             |
| Enger et al, 2014    | ORD, USA          | Cohort study                    | Optum Research Database (insurance plans)                                    | 90,931         | 534      | 56,740 (62%) | 49                         | 2000-06      | Seropositive             | Myocardial infarction, stroke       |
| Gilles et al, 2014   | OCS, Canada       | Cohort study                    | Clinic register                                                              | 4152           | 167      | 3483 (84%)  | 36                         | 1995-2011    | Seropositive             | Cardiovascular disease†             |
| Hsu et al, 2014      | Taiwan            | Cohort study                    | National Health Insurance Research Database                                 | 7055           | 429      | 4599 (65%)  | 54.9                       | 2003-11      | Seropositive             | Myocardial infarction, stroke       |
| Pothineni et al, 2014 | UAMS, USA         | Cohort study                    | Enterprise Data Warehouse at University of Arkansas for Medical Sciences      | 230,90         | 951      | 12,631 (55%) | 50.9                       | 2001-13      | Viraemic                | Cardiovascular disease†             |
| Tripathi et al, 2014 | USA               | Cohort study                    | Medicaid                                                                     | 13,632         | 1284     | 7661 (56%)  | 38                         | 1994-2011    | Seropositive             | Cardiovascular disease              |
| Womack et al, 2014   | Veterans Aging Cohort Study—virtual cohort, USA | Cohort study                    | Veterans Health Administration, Medicare, Medicaid, and Quality Enhancement Research Initiative in ischaemic heart disease | 2187           | 86       | 0 (43.6)    | 43.6                       | 2003-09      | Seropositive             | Cardiovascular disease†             |
| Adinolfi et al, 2015 | Italy             | Case-control study              | Hospital records                                                             | 820            | 123      | 524 (64%)  | 76                         | 2010-12      | Seropositive             | Stroke                              |
| Hsu et al, 2013      | LHID2000, Taiwan  | Cohort study                    | Longitudinal Health Insurance Database 2000                                 | 15,565         | NR       | 8078 (52%)  | Not reported               | 2004-07      | Viraemic                | Stroke                              |
| Younossi et al, 2013 | NHANES III, USA   | Cohort study                    | National Health and Nutrition Examination Survey                              | 8,985          | NR       | 4178 (66%)  | Not reported               | 1988-2006    | Viraemic                | Cardiovascular disease              |
| Campbell et al, 2012 | UK                | Cohort study                    | Hospital records                                                             | 4068           | 32       | 4068 (100%) | 36.5                       | 2004-09      | Seropositive             | Cardiovascular disease†             |
| Carriero et al, 2012 | APROCO-COPILOTE   | France Cohort study             | Medical questionnaires                                                       | 1154           | 49       | 900 (78%)  | 37.7                       | 1997-2010    | Seropositive             | Cardiovascular disease†             |

*ICD-9, ICD-10, ICD-11: International Classification of Diseases.*

*(Table continues on next page)*
(Continued from previous page)

| Cohort name | Country or region | Study type | Data source | Participants, n | Events, n | Men, n (%) | Mean age at baseline, years | Study period | Hepatitis C virus status | Outcome definition |
|-------------|-------------------|------------|-------------|-----------------|-----------|------------|--------------------------|--------------|-----------------------|------------------|
| Forde et al, 2012 | THIN | UK | Cohort study | General practice medical records | 76477 | 264 | 46727 (61%) | 38 6 | 1996-2008 | Undefined | Myocardial infarction | Read diagnostic code |
| Lee et al, 2012 | REVEAL-HCV | Taiwan | Cohort study | Questionnaires and interviews | 19636 | 477 | 9523 (48%) | 47 6 | 1991-2008 | Viraemic | Cardiovascular disease | ICD-9 |
| Liao et al, 2012 | NHIRD | Taiwan | Cohort study | National Health Insurance Research Database | 20470 | 1981 | 10235 (50%) | 52 | 2002-08 | Viraemic | Stroke | ICD-9 |
| Freiberg et al, 2011 | Veterans Aging Cohort Study-virtual cohort | USA | Cohort study | Veterans Aging Cohort Study and Large Health Study of Veteran Enrollees | 8579 | 194 | 8579 (100%) | 48 1 | 2000-07 | Seropositive | Cardiovascular disease* | ICD-9 |
| Kristiansen et al, 2011 | Norway | Cohort study | Department of Microbiology, University Hospital of North Norway | 1010 | 5 | 686 (68%) | 40 | 1990-2000 | Seropositive | Cardiovascular disease | ICD-10 |
| Ohsawa et al, 2011 | KAREN | Japan | Cohort study | KAREN cohort | 1077 | 194 | 682 (63%) | 60 4 | 2003-08 | Seropositive | Cardiovascular disease | ICD-10 |
| Bedimo et al, 2010 | HIV Clinical Care Registry | USA | Cohort study | Veterans Registry | 19424 | 1146 | 18938 (97%) | 46 2 | 1984-2004 | Viraemic | Myocardial infarction, stroke* | ICD-9 |
| Bellosso et al, 2010 | LATINA | Brazil, Mexico | Cohort study | LATINA cohort | 160 | 40 | Not reported | Not reported | 1997-2007 | Seropositive | Cardiovascular disease* | Physician diagnosis |
| DAD Study Group, 2010 | DAD study | Europe, USA, Australia | Cohort study | DAD cohort | 21815 | 517 | 16143 (74%) | 38 | 1999-2007 | Seropositive | Myocardial infarction* | WHO MONICA Project |
| Lee et al, 2010 | Taiwan | Cohort study | National Death Certification Registry | 23665 | 22 | 11879 (50%) | 47 1 | 1991-92 | Viraemic | Stroke | ICD-9 |
| Tusi et al, 2009 | The Heart and Soul study | USA | Cohort study | Veterans Administration electronic records | 981 | 151 | 803 (82%) | 66 3 | 2000-06 | Seropositive | Cardiovascular disease | Physician diagnosis |
| Guilman et al, 2008 | USA | Cohort study | Blood Systems | 20518 | 88 | 13254 (65%) | Not reported | 1991-2002 | Seropositive | Cardiovascular disease | ICD-9 CM, ICD-10 CM |
| Kalantar-Zadeh et al, 2000 | USA | Cohort study | DaVita outpatient dialysis database | 13664 | NR | 7433 (54%) | 60 1 | 2001-04 | Seropositive | Cardiovascular disease | Undefined |
| Ancarli et al, 2006 | USA | Case-control study | Clinical registry | 75834 | 292 | 47775 (63%) | 40 2 | 1991-2000 | Seropositive | Myocardial infarction | ICD-9 |
| Amin et al, 2006 | Australia | Cohort study | New South Wales Health Department Notifiable Diseases Database | 582 | 450 | 582 (100%) | 34 | 1990-2002 | Seropositive | Cardiovascular disease | ICD-9 and ICD-10 |

ICD=International Classification of Diseases. ERCHIVES=Electronically Retrieved Cohort of Hepatitis C Virus Infected Veterans. DOPPS=Dialysis Outcomes and Practice Patterns Study. NHIRD-HCV=National Health Insurance Research Database-Hepatitis C Virus. ORD=Optum Research Database. OCS=Ontario HIV Treatment Network Cohort Study. UAMS=University of Arkansas for Medical Sciences. LHD2000=Longitudinal Health Insurance Database 2000. NR=not reported. NHAMES III=National Health and Nutrition Examination Survey III. APPOCO-COPILOTE=Aprotinin =cohort. THIN=The Health Improvement Network. REVEAL=HCV-Risk Evaluation of Vical Load Elevation and Associated Liver Disease/Cancer-Hepatitis C Virus. DAD=Data Collection on Adverse Events of Anti-HIV Drugs. MONICA=Multinational Monitoring of Trends and Determinants in Cardiovascular Disease. CM=Clinical Modification. *Risk ratio reported for hepatitis C virus and HCV coinfection versus HIV infection only. †Australia, Belgium, Canada, mainland China, France, Germany, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Italy, Japan, New Zealand, Spain, Russia, Sweden, Turkey, the UK, and the USA.

Table: Baseline characteristics of studies included in the meta-analysis

Individuals with HCV had a higher risk of cardiovascular disease than individuals without HCV (pooled RR 1.28, 95% CI 1.18–1.39; figure 2). When stratified by outcome the risk ratio was 1.13 (95% CI 1.00–1.28) for myocardial infarction, 1.38 (1.19–1.60) for stroke, and 1.39 (1.24–1.55) for cardiovascular mortality (appendix p 11). Individuals with HCV and HIV co-infection had a higher risk of cardiovascular disease than those with HIV mono-infection (RR 1.20, 1.09–1.32). Post-hoc analyses showed that the RR estimates from studies published before 2014, which was the median publication year, were marginally higher than those from studies published...
Figure 2: Forest plots of pooled RRs for cardiovascular disease in people with hepatitis C virus versus people without.

Risks were pooled across studies using a random effects model (DerSimonian-Laird method).

### Cardiovascular events

#### A. Cardiovascular events

| Study                        | n/N          | RR (95% CI)     |
|------------------------------|--------------|-----------------|
| Amin et al (2006)7           | 450/75834    | 1.30 (1.20–1.50) |
| Kalantar-Zadeh et al (2007)53 | 34/664       | 1.14 (0.94–1.36) |
| Guiltnan et al (2008)43      | 88/19518     | 2.21 (1.41–3.46) |
| Tsui et al (2009)31          | 151/981      | 1.74 (0.92–3.32) |
| Bellaso et al (2010)11       | 40/160       | 2.64 (0.65–10.80)|
| Freiberg et al (2011)4       | 129/8579     | 1.15 (0.77–1.71) |
| Freiberg et al (2013)31      | 65/8579      | 1.60 (1.03–2.48) |
| Kristiansen et al (2011)37   | 5/1010       | 1.18 (0.38–2.74) |
| Ohsawa et al (2011)35        | 194/1077     | 1.33 (0.84–2.11) |
| Lee et al (2012)8            | 477/1956     | 1.53 (1.05–2.23) |
| Carrieri et al (2012)20      | 49/1354      | 1.36 (0.67–2.69) |
| Younossi et al (2013)39      | NR/701       | 0.71 (0.23–2.11) |
| Younossi et al (2013)39      | NR/8284      | 1.44 (0.97–2.13) |
| Freiberg et al (2011)56      | 167/4153     | 1.32 (0.98–1.76) |
| Tripathi et al (2011)29      | 1284/43625   | 1.22 (0.98–1.53) |
| Womack et al (2014)27        | 86/2187      | 1.10 (0.98–1.22) |
| Fernandes-Montero et al (2015)50 | 29/1066 | 1.51 (1.72–3.41) |
| Alvaro-Meca et al (2015)7     | 129/4972     | 1.40 (0.90–1.93) |
| Piazza et al (2016)38        | 19/143       | 0.19 (0.08–0.54) |
| Goodkin et al (2017)30       | 6790/7689    | 1.10 (0.60–2.00) |
| Chew et al (2017)41          | 11731/18825  | 0.96 (0.90–1.02) |
| Kovaniet al (2017)32         | 1433006      | 0.90 (0.60–1.34) |
| Heo et al (2018)33           | 1172728      | 1.40 (0.97–2.02) |
| **Pooled (I²:59.9%)**        |              | 1.28 (1.15–1.42) |

### Myocardial infarction

#### B. Myocardial infarction

| Study                        | n/N          | RR (95% CI)     |
|------------------------------|--------------|-----------------|
| Ancari et al (2006)7         | 292/522      | 0.94 (0.52–1.68) |
| Bedimo et al (2010)10        | 278/19424    | 1.25 (0.98–1.61) |
| DAD study group (2010)28     | 517/21815    | 0.86 (0.62–1.19) |
| Forde et al (2012)9          | 264/7478     | 1.10 (0.67–1.81) |
| Campbell et al (2012)21      | 32/4088      | 3.94 (0.00–15.50)|
| Enger et al (2014)30         | 473/9931     | 0.94 (0.73–1.20) |
| Pothiner et al (2014)35      | 952/16233    | 1.95 (1.33–2.90) |
| Hsu et al (2016)41           | 230/755      | 0.95 (0.38–2.37) |
| Tsai et al (2015)35          | 848/69195    | 1.25 (0.63–2.51) |
| Butt et al (2017)11          | 340/112562   | 0.93 (0.87–1.09) |
| Butt et al (2017)11          | 16844404     | 1.13 (1.02–1.25) |
| Butt et al (2017)11          | 77615265     | 1.19 (1.01–1.43) |
| Goodkin et al (2017)30       | 22087689     | 1.05 (0.88–1.25) |
| **Pooled (I²:77.6%)**        |              | 1.13 (1.00–1.28) |

### Stroke

#### C. Stroke

| Study                        | n/N          | RR (95% CI)     |
|------------------------------|--------------|-----------------|
| Bedimo et al (2010)71        | 86813424     | 1.20 (1.04–1.39) |
| Lee et al (2010)48           | 1621665     | 2.36 (1.42–3.93) |
| Lee et al (2010)48           | 621665      | 2.82 (1.25–6.37) |
| Liao et al (2012)21          | 19820740    | 1.22 (1.13–4.09) |
| Adinolfi et al (2013)38      | 123820      | 2.04 (1.69–2.46) |
| Hsu et al (2013)33           | 9153565     | 1.23 (1.06–1.42)|
| Enger et al (2014)30         | 11109033    | 1.76 (1.23–2.57) |
| Hsu et al (2014)48           | 1977055     | 0.93 (0.67–1.26) |
| Goodkin et al (2017)30       | 20747689    | 1.08 (0.92–1.27) |
| Alvaro-Meca et al (2017)7     | 464091      | 1.24 (0.51–3.05) |
| Alvaro-Meca et al (2017)7     | 774091      | 1.09 (0.59–2.00) |
| Alvaro-Meca et al (2017)7     | 914091      | 1.48 (0.90–2.45) |
| Alvaro-Meca et al (2017)7     | 1534091     | 1.06 (0.73–1.53) |
| **Pooled (I²:75.3%)**        |              | 1.38 (1.19–1.60) |
| **Overall (df=46; I²:77.5%)** |              | 1.28 (1.18–1.39) |
After 2014 (1.39 [1.25–1.54] vs 1.22 [1.11–1.34]), Studies that ascertained outcome with physician diagnosis had higher RRs than did those that used International Classification of Diseases codes (1.68 [1.24–2.29] vs 1.31 [1.20–1.42]). Compared with studies with a low risk of bias, those with moderate or high risk of bias had a similar pooled RR (1.30 [1.10–1.55] for studies with moderate or high risk of bias vs 1.29 [1.19–1.40] for studies with low risk of bias).

There was significant heterogeneity ($I^2=77.5\%$) and publication bias in the overall estimate (Egger’s test $p=0.003$). Using the trim and fill method to correct for funnel plot asymmetry did not change the direction of effect but did attenuate the effect size (appendix p 20). 11 studies were at moderate or high risk of bias (appendix pp 12, 13). Compared with studies with a low risk of bias, those with moderate or high risk of bias had a similar pooled RR (1.30 [95% CI 1.10–1.55] for studies with moderate or high risk of bias vs 1.29 [1.19–1.40] for studies with low risk of bias).

We estimated that in 2015, 1.5 million (95% CI 0.9–2.1) DALYs from cardiovascular disease were attributable to HCV, with marked geographical variation in the estimated burden. LMICs had the highest disease burden, with South Asia, eastern Europe, North Africa, and the Middle East accounting for nearly two-thirds of the global burden of cardiovascular disease attributable to HCV in 2015 (920.7 thousand DALYs; appendix p 14).

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Of the 100 countries with available age-specific and sex-specific viraemic HCV prevalence estimates for 2015, the highest burden (ie, cardiovascular DALYs attributable to HCV) was in Ukraine, Mongolia, Gabon, and Egypt (figure 3; appendix pp 15–17). Worldwide, the PAF of cardiovascular disease attributable to HCV was highest in people aged 55–59 years (appendix p 18). DALYs from cardiovascular disease attributable to HCV was highest in people aged 70–74 years (appendix p 18). The burden of cardiovascular disease attributable to HCV was higher in LMICs than in high-income countries (1.4 million [95% CI 0.88–1.95] DALYs vs 0.1 million [95% CI 0.07–0.12] DALYs; figure 4; appendix p 19).
Discussion

In this systematic review and meta-analysis, we assessed the association between HCV and cardiovascular disease and estimated the global, regional, and national burden of cardiovascular disease attributable to HCV. We made several key observations. First, people with HCV have an increased risk of cardiovascular disease compared with those without HCV (RR 1.28). When stratified by type of cardiovascular event, the overall pooled estimate was higher for stroke than for myocardial infarction. Second, our pooled risk estimate was derived from 341739 people with HCV infection included in 36 studies from 51 countries. Only two studies reported findings from populations of LMICs, highlighting the paucity of data from these regions. Third, the most up-to-date annual global burden of cardiovascular disease attributable to HCV was 1.5 million DALYs. Most of this burden was concentrated in the 55–75 year age group, reflecting a higher risk for cardiovascular disease among people with HCV. Fourth, considerable geographical variation was identified in the burden of cardiovascular disease attributable to HCV, with the highest burden observed in south Asia, eastern Europe, north Africa, and the Middle East. The majority of the burden was borne by LMICs rather than high-income countries. This observation is likely to reflect both a high prevalence of chronic hepatitis C in these regions and an increasing burden of cardiovascular disease.

Our analysis has several strengths. We included longitudinal studies that evaluated the association between HCV and hospital admissions with, or mortality from, cardiovascular disease. Furthermore, the endpoint of our analysis was major adverse cardiovascular events, which enabled accurate risk estimation and assessment of cardiovascular burden. Previous systematic reviews and meta-analyses which included cross-sectional studies and studies that used surrogate endpoints that might not be fully reflective of a causal relationship, have reported divergent findings. We also analysed burden using age-specific, sex-specific, and country-specific cardiovascular burden and HCV prevalence estimates, allowing us to provide HCV attributable burden estimates for specific age groups, which could be useful for policy makers. Moreover, our estimates for HCV prevalence obtained from the Polaris Observatory reflect viraemia rather than just seropositivity alone, and the countries for which we had prevalence estimates accounted for over 89% of all chronic HCV infections globally. Our estimates for the PAF and subsequent HCV associated cardiovascular burden are therefore based on a high-risk population with active HCV infection, in whom both long-term hepatic and extrahepatic complications remain common.

This study has a number of limitations. Most studies included in this meta-analysis originated from high-income countries in North America and western Europe, but estimates were applied to all regions. This approach is commonly used in this type of analysis because of the paucity of data from LMICs. This highlights an ongoing need for research in these low-resource settings, in which the disease prevalence of HCV and cardiovascular disease is high, to improve the accuracy of the burden estimates in these regions. We also observed significant heterogeneity in our RR estimates. However, the direction of effect was consistent and robust across all subgroup analyses. The observed heterogeneity is likely to reflect the diverse patient population, viraemic status of the study population, differences in health-care systems, access to treatment, and geographical location of the studies pooled in this analysis. Many studies did not fully account for the competing risk of non-cardiovascular mortality, thus some methodological heterogeneity exists. Most people with HCV infection die from non-cardiovascular causes, therefore this is an important competing risk that might distort the exposure-outcome association with cardiovascular disease. People with HIV and HCV co-infection have a higher risk for cardiovascular disease than those with HIV mono-infection. This increased risk highlights the importance of risk stratification in this patient population considering that people with HIV are twice as likely to have cardiovascular events than those without HIV. Although most studies evaluating the RR of cardiovascular disease adjusted for risk factors for cardiovascular disease, a substantial possibility of residual confounding remains. Furthermore, there was substantial publication bias in the literature, which might have influenced the risk estimates. However, there was little attenuation of the RR when analysis was restricted to studies without moderate to high risk of bias or after accounting for publication bias using the trim and fill method. Additionally, we pooled RR estimates of myocardial infarction or stroke to estimate the PAF and combined this with the DALYs for ischaemic heart disease and cerebrovascular disease to estimate the burden of cardiovascular disease attributable to HCV. We were unable to estimate the burden of angina or peripheral artery disease attributable to HCV since these conditions are often diagnosed in the outpatient setting and are less likely to be captured by electronic health record systems. Therefore, it is possible that we have underestimated the cardiovascular burden associated with HCV. However, the 2010 Global Burden of Disease study showed that angina and peripheral artery disease contributed a relatively small proportion of the overall cardiovascular disease burden. The studies included in this meta-analysis are likely to be exposed to a degree of outcome misclassification bias because most studies used routine diagnostic coding to define cardiovascular events rather than clinical adjudication. All of the included studies were observational studies, and thus we are unable to establish causality.

The underlying pathophysiological mechanism for the association between HCV and cardiovascular disease...
remains unclear.\textsuperscript{25} HCV infection has been associated with conditions such as type 2 diabetes, a well-known cardiovascular risk factor.\textsuperscript{26} Evidence has emerged showing direct effects of HCV on the development of atherosclerosis,\textsuperscript{27} beyond that attributable to metabolic derangements alone. Chronic HCV infection results in a chronic state of immune stimulation and inflammation evidenced by increased circulating levels of proinflammatory cytokines, such as interleukin 6, tumour necrosis factor-α, C-reactive protein, and fibrinogen, all of which are associated with the development of atherosclerotic cardiovascular disease.\textsuperscript{32,34,75} Interferon-based antiviral treatments for HCV reduce markers of inflammation, endothelial dysfunction, and diabetes mellitus.\textsuperscript{76–78} Sustained viral response with direct-acting antivirals have also been associated with a lower risk of cardiovascular events.\textsuperscript{79} Whether eradication of HCV infection reduces future risk of adverse cardiovascular events should be further explored in randomised controlled trials of direct-acting antivirals to investigate this finding.

The link between HCV and cardiovascular disease has important implications for the formulation of health policies and resource allocation, particularly in regions with limited health-care resources, where chronic HCV infection remains prevalent and cardiovascular disease burden is increasing. Globally, prevalence of HCV is projected to increase substantially, particularly in LMICs, as a result of transmission via unsafe health-care related injections and injection drug use.\textsuperscript{8,10} Consequently, mortality due to hepatic and extrahepatic complications of HCV is likely to increase considerably if efforts to improve early testing and treatment are not implemented. A disproportionate burden of cardiovascular disease is borne by LMICs, where currently more than 80% of the global burden is concentrated.\textsuperscript{80} Our estimates suggest that more than 90% of the global cardiovascular burden attributable to HCV occurs in LMICs.

The introduction of direct-acting antiviral therapies with the ability to achieve sustained virological response in more than 90% of treated individuals should be a cause for optimism. These new therapeutic options enable the prevention of both hepatic and extrahepatic complications of HCV infection with a shorter duration of treatment and fewer adverse events than previous generations of antiviral therapies. However, at present, public health programmes and access to health-care services for people with HCV lags behind other comparable infectious diseases, such as HIV or malaria.\textsuperscript{81} The provision of direct-acting antiviral therapies in patients with HCV infection remains low on the global scale, with only one in 15 patients currently being treated, the majority of whom reside in high-income countries.\textsuperscript{82,83} To have the greatest impact on HCV morbidity and mortality, the delivery of curative HCV treatment needs to be coupled with efficient health systems to provide chronic care services for patients with both hepatic and extrahepatic complications of HCV. Considering our study findings, investment in greater strategic integration and linkage of viral hepatitis services with other relevant services, including cardiovascular disease prevention, might be a cost-effective method of facilitating the prevention and management of concurrent major health conditions. These innovative approaches to health-care delivery might require further research to evaluate feasibility and efficacy in a real-world clinical setting.

People with HCV have a higher risk of developing cardiovascular disease than those without HCV. HCV accounted for 1·5 million DALYs due to cardiovascular disease worldwide in 2015, with the highest burden in South Asia, eastern Europe, north Africa, and the Middle East. Most of the disease burden is borne by LMICs, where HCV prevalence is projected to rise substantially. Our findings are of public health importance and could inform future research and health-care policies to improve risk stratification and treatment strategies aimed at reducing the combined global burden of HCV and extrahepatic sequelae such as cardiovascular disease.

Contributors

KKL, DS, and ASVS conceived and designed the study. KKL, DS, RB, MA, FS, SoB, and ASVS acquired the data. KKL and ASVS analysed and interpreted the data. KKL and ASVS drafted the initial manuscript. KKL, DS, RB, DEN, JSS, MHC, CSB, CTL, ShB, SK, SaB, HR, PRM, NLM, DAM, and ASVS critically reviewed the manuscript for intellectual content. All authors approved the final version of the report.

Declaration of interests

CTI reports grants from Gilead Sciences, outside the submitted work. SaB and HR report grants from Gilead and AbbVie, outside the submitted work. All other authors declare no competing interests.

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References

1. WHO. Global Hepatitis Report 2017 https://apps.who.int/iris/bitstream/handle/10665/255016/9789241565455-eng.pdf;jsessionid=d7364F80B821E480F3FCEF00F2D7D6C1?sequence=1 (accessed July 4, 2019).
2. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology 2015; 62: 1535–63.
3. Centers for Disease Control and Prevention. Surveillance for viral hepatitis—United States, 2015. https://www.cdc.gov/hepatitis/statistics/2015surveillance/commentary.htm (accessed May 25, 2018).
4. Grebely J, Page K, Sacks-Davis R, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 2014; 59: 309–20.
5. Aspinall EJ, Hutchinson SJ, Janjua NZ, et al. Trends in mortality after diagnosis of hepatitis C virus infection: an international comparison and implications for monitoring the population impact of treatment. J Hepatol 2015; 62: 269–77.
6. Grebely J, Dore GJ. What is killing people with hepatitis C virus infection? Semin Liver Dis 2011; 31: 331–39.
7. Amin J, Law MG, Bartlett M, Kaldor JM, Dore CJ, Gaus C. Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. Lancet 2006; 368: 938–45.
and national age-sex specific mortality for 264 causes of death, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1151–210.

9 Loge S, Soyoglerel G, Fields R, Luby S, Hutin Y. Rapid assessment of injection practices in Mongolia. Am J Infect Control 2004; 32: 31–37.

10 Mohsen AA, Bernard A, LeFouler L, et al. Hepatitis C virus acquisition among Egyptians: a 10-year surveillance of acute hepatitis C. Trop Med Int Health 2015; 20: 89–97.

11 Luby SP, Qamaruddin K, Shah AA, et al. The relationship between therapeutic injections and high prevalence of hepatitis C infection in Hafizabad, Pakistan. Epidemiol Infect 1997; 115: 349–56.

12 Golia E, Limongelli G, Natale F, et al. Inflammation and cardiovascular disease: from pathogenesis to therapeutic target. Curr Atheroscler Rep 2014; 16: 415.

13 Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342: 836–43.

14 Welsch C, Efinger M, von Wagner M, et al. Ongoing liver inflammation in patients with chronic hepatitis C and sustained virological response. PLoS One 2012; 7: e417755.

15 Bahkiet A, Joudy J, Kli germann S, Khambaty M, Shah A, Bagchi S. Risk of cardiovascular disease due to chronic hepatitis C infection: a review. J Clin Transl Hepatol 2016; 5: 343–62.

16 Caochou P, Gragnani L, Cignone P, Carminati M, Zignego AL. Extramucosal manifestations of chronic hepatitis C virus infection. Dig Liver Dis 2014; 46 (suppl 5): S165–73.

17 Goossens N, Negro F. Cardiovascular manifestations of hepatitis C virus. Clin Liver Dis 2017; 21: 465–73.

18 Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. J Hepatol 2014; 61 (suppl 1): S69–78.

19 Momiyama Y, Ohmori R, Kato R, Taniguchi H, Nakamura H, Ohsuzu F. Lack of any association between persistent hepatitis B or C virus infection and coronary artery disease. Atherosclerosis 2005; 181: 211–13.

20 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6: e1000097.

21 Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. JAMA 2009; 321: 1295–303.

22 Shah ASV, Stezle D, Lee KK, et al. Global burden of atherosclerotic cardiovascular disease in people living with HIV. Circulation 2013; 138: 1100–12.

23 Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2013: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 161–76.

24 Institute for Health Metrics and Evaluation. GBD results tool. http://ghdx.healthdata.org/gbd-results-tool (accessed May 14, 2018).

25 Shah AS, Lee KK, McAllister DA, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. BMJ 2015; 350: h1295.

26 Shah AS, Langrish JP, Nair H, et al. Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 2013; 382: 1039–48.

27 World Bank. Bank world country and lending groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed May 23, 2018).

28 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–34.

29 Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000; 56: 455–63.

30 Goodkin DA, Bieber B, Jadoul M, Martin P, Kanda E, Pisoni RL. Mortality, hospitalization, and quality of life among patients with hepatitis C infection on hemodialysis. Clin J Am Soc Nephrol 2012; 7: 287–97.

31 Belloso WH, Orellana LC, Grinsztajn B, et al. Analysis of serious non-AIDS events among HIV-infected adults at Latin American sites. HIV Mol 2010; 11: 554–64.

32 Tsui JL, Whooley MA, Monto A, Seal K, Tien PC, Shlipak M. Association of hepatitis C virus seropositivity with inflammatory markers and heart failure in persons with coronary heart disease: data from the Heart and Soul study. J Cardiol Fail 2009; 15: 451–56.

33 Heo NY, Mannalithara A, Kim D, Udompap P, Tan JC, Kim WR. Long-term patient and graft survival of kidney transplant recipients with hepatitis C in the United States. Transplantation 2018; 102: 454–60.

34 Alvaro-Meca A, Berenguer J, Diaz A, et al. Stroke in HIV-infected individuals with and without HCV coinfection in Spain in the combination antiretroviral therapy era. PLoS One 2017; 12: e0179491.

35 Butt AA, Yan P, Chew KW, et al. Risk of acute myocardial infarction among hepatitis C virus (HCV)-positive and HCV-negative men at various lipid levels: results from ERCHIVES. Clin Infect Dis 2017; 65: 557–65.

36 Chew KW, Bhattacharya D, Horwich TB, et al. Performance of the pooled cohort atherosclerotic cardiovascular disease risk score in hepatitis C virus-infected persons. J Viral Hepat 2017; 24: 814–22.

37 Kovari H, Rauch A, Kouyou R, et al. Hepatitis C infection and the risk of non-liver-related morbidity and mortality in HIV-infected persons in the Swiss HIV Cohort Study. Clin Infect Dis 2017; 64: 490–97.

38 Piazza NA, Singal AK. Frequency of cardiovascular events and effect on survival in liver transplant recipients for cirrhosis due to alcoholic or nonalcoholic steatohepatitis. Hepatol Clin Transplant 2016; 14: 79–85.

39 Fernandez-Montero J, Barreiro P, de Mendoza C, Labarga P, Soriano V. Hepatitis C virus coinfection independently increases the risk of cardiovascular disease in HIV-positive patients. J Viral Hepat 2016; 23: 47–52.

40 Tsai MS, Hsu YC, Yu PC, Lin CL, Kao CH. Long-term risk of acute coronary syndrome in hepatitis C virus infected patients without antiviral treatment: a cohort study from an endemic area. Int J Cardiol 2015; 181: 27–29.

41 Vajdic CM, Mazari Pour S, Olivier J, et al. The impact of blood-borne viruses on cause-specific mortality among opioid dependent people: an Australian population-based cohort study. Drug Alcohol Depend 2015; 152: 266–71.

42 Enger C, Forssen UM, Bennet D, Theodore D, Shantakumar S, McAlee A. Thromboembolic events among patients with hepatitis C virus infection and cirrhosis: a matched-cohort study. Adv Ther 2014; 31: 891–903.

43 Gillis J, Smieja M, Cescon A, et al. Risk of cardiovascular disease associated with HCV and HIV coinfection among antiretroviral-treated HIV-infected individuals. Antivir Ther 2014; 19: 309–17.

44 Hsu YC, Lin JT, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatology 2014; 59: 1293–302.

45 Pothineni NV, Delongchamp R, Vallurupalli S, et al. Impact of hepatitis C seropositivity on the risk of coronary heart disease events. Am J Cardiol 2014; 114: 1841–45.

46 Tripathi A, Lieue AD, Winniford MD, et al. Impact of clinical and therapeutic factors on incident cardiovascular and cerebrovascular events in a population-based cohort of HIV-infected and non-HIV-infected adults. Clin Cardiol 2014; 37: 517–22.

47 Womack JA, Chang CC, So-Armah KA, et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc 2014; 3: e001035.

48 Adinolfi LE, Rastivo I, Guerrera B, et al. Chronic HCV infection is a risk factor of ischemic stroke. Atherosclerosis 2013; 231: 22–26.

49 Hsu CS, Kao JH, Chao YC, et al. Interferon-based therapy reduces risk of stroke in chronic hepatitis C patients: a population-based cohort study in Taiwan. Aliment Pharmacol Ther 2013; 38: 415–23.

50 Younoszi ZM, Zheng L, Stepanova M, Venkatesan C, Mir HM. Moderate, excessive or heavy alcohol consumption: each is significantly associated with increased mortality in patients with chronic hepatitis C. Aliment Pharmacol Ther 2013; 7: 303–9.

51 Campbell LJ, Desai M, Hegazi A, et al. Renal impairment is associated with coronary heart disease in HIV-positive men. HIV Clin Trials 2012; 13: 343–49.

52 Carriazo MP, Protopenescu C, Le Moing V, et al. Impact of immunodoppression and moderate alcohol consumption on coronary and other arterial disease events in an 11-year cohort of HIV-infected patients on antiretroviral therapy. BMJ Open 2012; 2: e001555.
53 Forde KA, Haynes K, Trexel AB, et al. Risk of myocardial infarction associated with chronic hepatitis C virus infection: a population-based cohort study. J Viral Hepat 2012; 19: 271–77.

54 Lee MH, Yung HI, Lu SN, et al. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. J Infect Dis 2012; 206: 469–77.

55 Liao CC, Su TC, Sung FC, Chou WH, Chen TL. Does hepatitis C virus infection increase risk for stroke? A population-based cohort study. PLoS One 2012; 7: e31527.

56 Freiberg MS, Chang CC, Skanderson M, et al. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. Circ Cardiovasc Qual Outcomes 2011; 4: 425–32.

57 Kristiansen MG, Lochen ML, Gutteberg TJ, Mortensen L, Eriksen BO, Florholmen J. Total and cause-specific mortality rates in a prospective study of community-acquired hepatitis C virus infection in northern Norway. J Viral Hepat 2011; 18: 237–44.

58 Ohashi M, Kato K, Tanno K, et al. Seropositivity for anti-HCV core antigen is independently associated with increased all-cause, cardiovascular, and liver disease-related mortality in hemodialysis patients. J Epidemiol 2011; 21: 491–99.

59 Bedimo RJ, Westfall AO, Mugavero MJ, Drechsler H, Khamra N, Saag MS. Hepatitis C virus coinfection and the risk of cardiovascular disease among HIV-infected patients. HIV Med 2010; 11: 462–68.

60 Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group, Weber R, Sabin C, et al. HBV or HCV coinfections and risk of myocardial infarction in HIV-infected individuals: the D:A:D Cohort Study. Antivir Ther 2010; 15: 1077–86.

61 Lee MH, Yung HI, Wang CH, et al. Hepatitis C virus infection and increased risk of cerebrovascular disease. Stroke 2010; 41: 2894–900.

62 Guiltinan AM, Kaidarova Z, Custer B, et al. Increased all-cause, liver, and cardiac mortality among hepatitis C virus-seropositive blood donors. Am J Epidemiol 2008; 167: 743–50.

63 Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, et al. Hepatitis C virus and death risk in hemodialysis patients. J Am Soc Nephrol 2007; 18: 1384–93.

64 Arcari CM, Nelson KE, Netski DM, Nieto FJ, Gaydos CA. No association between hepatitis C virus seropositivity and acute myocardial infarction. Clin Infect Dis 2006; 43: e53–56.

65 Petta S, Maida M, Macaluso FS, et al. Hepatitis C virus infection is associated with increased cardiovascular mortality: a meta-analysis of observational studies. Gastroenterology 2016; 150: 149–55.

66 Ambrosino P, Lupoli R, Di Minno A, et al. The risk of coronary artery disease and cerebrovascular disease in patients with hepatitis C: a systematic review and meta-analysis. Int J Cardiol 2016; 221: 746–54.

67 Wong RJ, Kanwal F, Younossi ZM, Ahmed A. Hepatitis C virus infection and coronary artery disease risk: a systematic review of the literature. Dig Dis Sci 2014; 59: 1586–93.

68 GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017; 377: 13–27.

69 Forouzanfar MH, Liu P, Roth GA, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA 2017; 317: 165–82.

70 Mahajan R, Xing J, Liu SJ, et al. Mortality among persons in care with hepatitis C virus infection: the Chronic Hepatitis Cohort Study (CHICoS). 2006–2010. Clin Infect Dis 2014; 58: 1055–61.

71 Moran AE, Forouzanfar MH, Roth GA, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation 2014; 129: 1493–501.

72 White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008; 49: 831–44.

73 Mostafa A, Mohamed MK, Saeed M, et al. Hepatitis C infection and clearance: impact on atherosclerosis and cardiometabolic risk factors. Gut 2010; 59: 1115–20.

74 Riordan SM, Skinner NA, Kurtovic J, et al. Toll-like receptor expression in chronic hepatitis C: correlation with pro-inflammatory cytokine levels and liver injury. Inflamm Res 2006; 55: 279–85.

75 Roed T, Kristoffersen US, Knudsen A, et al. Increased prevalence of coronary artery disease risk markers in patients with chronic hepatitis C—a cross-sectional study. Vasc Health Risk Manag 2014; 10: 55–62.

76 Chew KW, Hua I, Bhattacharya D, et al. The effect of hepatitis C virologic clearance on cardiovascular disease biomarkers in human immunodeficiency virus/hepatitis C virus coinfection. Open Forum Infect Dis 2014; 1:e00104.

77 Patera P, Jeffrey GP, MacQuillan G, et al. The association between chronic hepatitis C infection and cardiovascular risk. Intern Med J 2016; 46: 63–70.

78 Berenguer J, Rodriguez-Castellano E, Carrero A, et al. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. Hepatology 2017; 66: 344–56.

79 Nahon P, Bourcier V, Layese R, et al. Eradication of hepatitis C virus infection in patients with cirrhosis reduces risk of liver and non-liver complications. Gastroenterology 2017; 152: 142–56.

80 GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1459–544.

81 WHO. Progress report on access to hepatitis C treatment. 2018. https://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CHDS-2018.4-eng.pdf?sequence=1 (accessed July 4, 2018).

82 Vutien P, Jin M, Le MH, et al. Regional differences in treatment rates for patients with chronic hepatitis C infection: systematic review and meta-analysis. PLoS One 2017; 12: e0183811.