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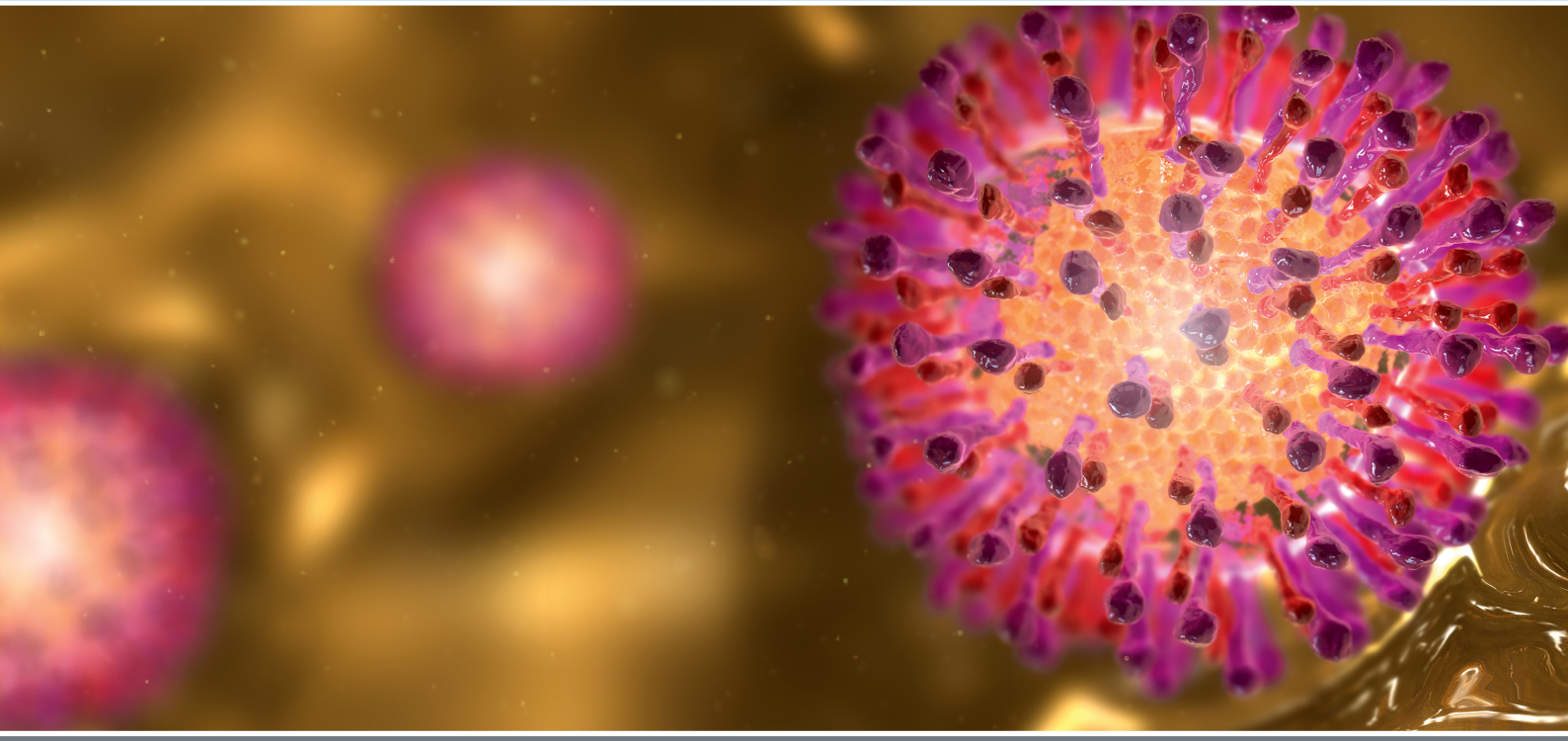
Depression, anxiety, pain and quality of life in people living with chronic hepatitis C

A systematic review and meta-analysis



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Contents

Abbreviations

ART	Antiretroviral treatment
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
CES-D	Centre for Epidemiologic Studies Depression Scale
CWP	Chronic widespread pain
DASS	Depression, Anxiety and Stress Scales
DH	Department of Health, UK
EHC	Extrahepatic condition
FS	Fibromyalgia syndrome
HBV	Hepatitis B virus
HCSUS	HIV Cost and Services Utilization Study (US)
HCV	Hepatitis C virus
HADS	Hospital Anxiety and Depression Scale
HDRS	Hamilton Depression Rating Scale
HRQOL	Health-Related Quality of Life
IFN	Interferon therapy
MCS	Mental component score of the SF36 HRQOL scale
MD	Mean difference
MOS	Medical Outcomes Study
NAFLD	Non-alcoholic fatty liver disease
NS	Not significant
OR	Odds ratio
PCR	Polymerase chain reaction
PCS	Physical component score of the SF36 HRQOL scale
PHQ-9	Patient Health Questionnaire version 9
PWID	People who inject drugs

RA	Rheumatoid arthritis
RNA	ribonucleic acid
RR	Risk ratio
SDS	Stress and Depression Scales
SSD	Statistically significant difference
STAI	State-Trait Anxiety Inventory
SVR	sustained viral response

Abstract

Objectives

Individuals infected with hepatitis C virus (HCV) can develop extrahepatic conditions which may have a significant impact on life expectancy and quality of life. We conducted a systematic review to assess the causal relationship between HCV and extrahepatic conditions and the impact of HCV upon health-related quality of life of people in the UK.

Methods

HCV advocacy groups identified conditions that they thought most important to research, and the perspectives of various stakeholders informed the scope of the review. A comprehensive literature search of a range of electronic databases and websites was undertaken. Screening, quality assessment and data extraction were conducted using specialist software. The key criterion for inclusion in a synthesis was a study's testing of the association between HCV and either quality of life or conditions specified as important by advocacy groups: depression, anxiety or painful conditions. Other criteria relating to study populations, measures and matching of study groups were also applied. Two reviewers assessed included studies, with disagreements resolved by a third reviewer where necessary. Studies were assessed for methodological quality using standardised appraisal tools. Meta-analyses were performed. Based on the consistency and sufficiency of research evidence, the findings were graded as strong, promising, tentative or inconclusive.

Results

71 studies were included in the review's syntheses. All studies were judged to be at a moderate or high risk of bias. Only two UK studies met our inclusion criteria.

Quality of life

Evidence from 22 studies indicates that people with HCV have worse quality of life than 'general' or 'healthy' populations; meta-analysis of nine studies indicated that the physical (PCS) and mental health (MCS) domains of quality of life on the Health-Related Quality of Life Scale were both statistically and clinically worse among HCV-infected people (PCS: MD 5.54, 95% CI 3.73-7.35, MCS: MD 3.81, 95% CI 1.97-5.64). Evidence from seven included studies suggests that people co-infected with HCV and HIV have worse quality of life than individuals with HIV only; meta-analysis of five studies indicated that both the physical and mental health domains of quality of life were significantly worse among people who were co-infected (PCS: MD 2.57, 95% CI 1.08-4.06, MCS: MD 1.88, 95% CI 0.06-3.69).

Depression and anxiety

Evidence from 22 studies indicates that depression and anxiety are more severe, and depression is more common among people with HCV compared to those without it. Meta-analysis of 12 studies identified the severity of depression in people with HCV to be significantly greater than in those without HCV (Mean

difference 0.98, 95% CI 0.43-1.53). Meta-analysis of nine studies identified the severity of clinical anxiety to be significantly greater among people with HCV (Mean difference 0.47, 95% CI 0.09-0.86). Meta-analysis of seven studies identified participants with HCV to be approximately three times more likely to be depressed compared to those without HCV (OR 2.77, 95% CI 1.62-4.74). No statistically significant evidence that anxiety is more common among people with HCV was found.

Pain

Evidence was appraised from 26 studies on painful conditions. A meta-analysis of four studies indicates that people with HCV are 17% more likely to suffer from arthralgia than those without HCV (RR 1.17, 95% CI 1.04-1.31). A meta-analysis of five studies suggested that people with HCV are significantly more likely to suffer from fibromyalgia; key differences across the studies in terms of the health status (co-morbidities) of HCV patients and comparison groups mean it is not possible to quantify the increased risk attributable to HCV. Other studies, including those on arthritis, were not amenable to meta-analysis.

Conclusions: Evidence suggests an association between HCV infection and depression, anxiety, fibromyalgia, arthralgia and health-related quality of life. However, the evidence was graded as ‘promising’ or ‘tentative’ rather than ‘strong’. More high-quality research on the association between HCV and these conditions is needed.

Executive summary

Background

Hepatitis C (HCV) is a viral condition that can be acute or chronic and is mainly transmitted via infected blood directly entering the bloodstream. Most people infected in Britain acquire the virus through unsterile drug injecting practices (Public Health England 2013). However, during the 1970s and 1980s, prior to the introduction of an effective blood donor screening test in 1991, an estimated 32,500 people in the UK were infected following blood transfusion or other medical procedures (Department of Health 2011). Infection typically results in chronic liver inflammation (hepatitis) but the consequences of contracting HCV are wide-ranging and can have a marked effect on the health of infected individuals. An estimated 1-2% of people infected will develop extrahepatic manifestations (Chen and Morgan 2006), which can be mild to severe and have a significant impact on both life expectancy and quality of life. In order to assess the causal relationship between HCV and extrahepatic conditions and the impact of HCV upon the health-related quality of life of people in the UK, the Department of Health in England called for evidence in the form of a comprehensive systematic review.

Aims

To inform policy and practice relating to people in the UK living with chronic HCV, this systematic review addressed the following questions:

- In general, how is chronic HCV infection associated with health-related quality of life?
- Which extrahepatic conditions are associated with chronic HCV infection?
- What is the strength of the relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?
- Which groups of people with chronic HCV are affected by extrahepatic conditions? Are there any moderating factors (e.g. age, sex, co-morbidity, iatrogenic acquisition, ethnicity, lifestyle risks) that influence the strength of any relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?
- Are there any mediating factors (e.g., co-morbidity, socio-economic factors, lifestyle factors) that might explain any observed significant relationship between extrahepatic conditions and health-related quality of life?

Methods

Stakeholder involvement

The perspectives of various stakeholder groups informed the scope and methods of the review. A number of advocacy groups were consulted on a group-by-group basis to identify the extrahepatic conditions that they felt were most important to research and to provide information about how these conditions might impact on quality of life. Other key experts, including NHS and DH health policy advisers,

epidemiologists, virologists, hepatologists, and representatives from other advocacy groups were contacted to provide their views through a scientific advisory group. The role of this group was to: help identify relevant datasets and studies for analysis; provide further contextual understanding of extrahepatic conditions related to HCV; advise on the review's research questions; help focus the scope of the review in order to determine which studies were included in the analysis; and comment on the initial findings and the final report.

Identification of evidence

Comprehensive searching was undertaken on a range of international and regional health and social science databases, and was supplemented by website searching.

Screening, quality assessment and data extraction were conducted using specialist software EPPI-Reviewer (Thomas et al. 2010). Two reviewers assessed included studies, with disagreements resolved by a third reviewer where necessary. Text mining software was used to identify the references most likely to be included and prioritise these for screening. A two-stage review was conducted, comprising a descriptive map and in-depth syntheses.

Describing the research field

An initial set of 'map' inclusion criteria were developed and applied to titles and abstracts in order to identify studies examining associations between HCV and quality of life, or HCV and any extrahepatic condition (EHC). A small number of descriptive codes were applied to all studies meeting these inclusion criteria; these helped to produce a systematic map that described the nature and extent of the research on quality of life and any EHC identified as relevant by that time, and so inform advisory group discussions about the feasibility and appropriateness of potential syntheses.

Appraising and synthesising the evidence

Following consultations with Advocacy groups and our Scientific Advisory Group, a further set of 'synthesis' inclusion criteria were devised and applied to identify studies on quality of life and priority EHCs that were suitable for synthesis. All included studies were assessed for methodological quality, using standardised risk of bias assessment tools. Where sufficient data were available, meta-analyses were performed. All statistical analyses were undertaken using R software. The overall strength of conclusions was then graded based on two considerations: the consistency and sufficiency of the evidence base.

Key findings

The state of the evidence base

The systematic map presented to our scientific advisory group showed that 194 EHCs had been studied as possibly being associated with HCV infection. It was therefore necessary to focus on a subset of the total. Four health states had been identified as important in all four of the consultations with advocacy groups, so in addition to studies examining the association between quality of life and HCV, we

examined three of these: depression, anxiety and pain. The most frequently researched conditions that were identified through the map included depression, as well as diabetes, non-Hodgkin's lymphoma, mixed cryoglobulinaemia, cognitive dysfunction, insulin resistance and lichen planus. Depression and anxiety were discussed together by advocacy group members, and tended to be examined together within studies.

Generally, the located evidence used for our syntheses was not strong for our particular review's research questions. In particular, in most studies, comparison groups of people with and without HCV were not matched, and potentially confounding factors were not considered or taken into account during the studies' analyses. However, we found promising evidence of an association between HCV infection and health-related quality of life, and between HCV and depression, anxiety, arthralgia and fibromyalgia.

There was a lack of high-quality UK-based studies available, with a single UK-based study included in each of the quality of life (Foster et al. 1998) and pain (Isaacs et al. 2013) syntheses, and no UK-based studies included in the depression and anxiety synthesis. Two multinational studies on quality of life included UK samples, but these studies did not provide UK-specific findings (Vietri et al. 2013; Ware et al. 1999).

Quality of life and hepatitis C infection

Findings from 22 studies with high or moderate risk of bias provided promising evidence that people with HCV had a poorer quality of life than 'general' or 'healthy' populations; the findings suggest that the impairment is both statistically and clinically significant. Meta-analysis of nine studies showed the physical (PCS) and mental health (MCS) domains of quality of life to be significantly worse among HCV-infected compared to uninfected individuals (PCS: MD 5.54, 95% CI 3.73-7.35, MCS: MD 3.81, 95% CI 1.97-5.64). Quality of life was reduced in both HCV patients with an iatrogenic infection and with a non-iatrogenic infection when compared to those without HCV; the deficit appeared to be of a similar magnitude in both types of HCV groups. Seven included studies provided tentative evidence to indicate that people who were co-infected with HCV and HIV had worse quality of life than people infected with HIV alone. Meta-analysis of five studies indicated that both the physical and mental health domains of quality of life were significantly worse among people who were co-infected (PCS: MD 2.57, 95% CI 1.08-4.06, MCS: MD 1.88, 95% CI 0.06-3.69).

Depression, anxiety and hepatitis C infection

Findings were drawn from 22 studies examining the association between HCV and depression and anxiety. The evidence indicates that depression and anxiety are more severe and depression is more common among people with HCV compared to people without it. Meta-analysis of 12 studies provided 'promising' evidence that the severity of depression in people with HCV is significantly greater than among those without HCV (mean difference 0.98, 95% CI 0.43-1.53). Meta-analysis of nine studies provided promising evidence that the severity of clinical anxiety is

significantly greater among people with HCV (mean difference 0.47, 95% CI 0.09-0.86). Meta-analysis of seven studies provided promising evidence that participants with HCV are approximately three times more likely to be depressed compared to those without HCV (OR 2.77, 95% CI 1.62-4.74). No statistically significant evidence was found that anxiety is more common among people with HCV.

Pain and hepatitis C infection

Findings from 26 studies with high or moderate risk of bias on the association between pain and HCV were examined. We found promising evidence that being infected with HCV is associated with an increase in the prevalence of fibromyalgia and arthralgia; evidence indicates no association between HCV and arthritis, but this finding is tentative.

A meta-analysis of four studies comparing arthralgia prevalence between people with and without HCV infection suggested that being infected with HCV is associated with a 17% increase in the prevalence of arthralgia (RR 1.17, 95% CI 1.04-1.31). However, it is possible that the observed results may be due to confounding in the observational studies examined. A meta-analysis of five studies suggested that people with HCV are significantly more likely to suffer from fibromyalgia; key differences across the studies in terms of the health status (co-morbidities) of HCV patients and comparison groups mean that it is not possible to quantify the increased risk attributable to HCV infection. Other studies were not amenable to meta-analysis, and studies with a high risk of bias were not considered in narrative analyses. Available evidence from just one suitable study with a moderate risk of bias showed no significant association between arthritis and HCV. Three studies with a moderate risk of bias examined different extrahepatic pain outcomes (joint pain, presence of fibromyalgia and pain intensity) in patients with varying degrees of liver disease severity. Each of the individual studies failed to demonstrate a relationship between severity of liver disease and extrahepatic pain or painful conditions. Only one study was found that compared pain in people co-infected with HIV and HCV with those infected with HIV alone. Here, the odds of muscle or joint pain were elevated amongst those co-infected with HCV, but the findings were not statistically significant.

Discussion

Overall, the findings from this systematic review suggest that HCV is associated with poorer quality of life and increases in depression, anxiety and the pain conditions fibromyalgia and arthralgia. The evidence base in not well developed for our review's research questions: lack of equivalence between HCV and comparison groups was a common feature, such that individual findings are graded as 'promising' or 'tentative' rather than 'strong'.

The findings of this review indicate a level of concordance between the focus of scientific research and the conditions identified as most pertinent to people living with HCV as identified by advocacy group representatives.

While the literature identified a focus on a range of medical conditions such as diabetes, cardiovascular conditions and autoimmune disorders, it also focused on a

range of neurological conditions such as depression, anxiety, pain, cognitive function and fatigue that members of patient advocate groups identified as key conditions impacting on the quality of life of people with HCV. In fact, neurological conditions were the most frequently researched extrahepatic conditions. However there appears to be a mismatch with regard to painful conditions, as these constituted only the eighth most commonly researched condition type in our map. The extrahepatic conditions identified as important by advocacy group members also differed from those of interest to some members of our Scientific Advisory Group.

The brief examination of the National Hepatitis C Register that we were able to undertake provided some promising insights into future research examining longitudinal data from identified people with hepatitis C; this offers a promising way to understand morbidity and mortality in the population most relevant to this review.

It should also be considered that the patient advocacy groups do not necessarily represent all of the population of interest. It could be that the majority of those iatrogenically infected with HCV are experiencing other extrahepatic conditions which are impacting on their quality of life. Short of undertaking a survey of all identified people with hepatitis C, the National Hepatitis C Register is the closest source of prospectively collected data available which may answer the question of which extrahepatic conditions are associated with morbidity and mortality in this population.

There is an apparent set of links between HCV, depression, anxiety and quality of life that merits further research and consideration by professionals working with people infected with HCV and potential HCV patients, e.g. counsellors might recognise the potential for increased support to cope with these extrahepatic conditions and tailor advice and referrals accordingly.

Strengths of our review

- This systematic review and meta-analysis represents the most comprehensive effort to date to ensure equivalency on at least some key variables which could also account for the association between HCV and extrahepatic conditions or quality of life.
- It has been conducted according to explicit and reproducible methods to ensure transparency and limit bias. It has also considered the equivalence of sample and comparison groups across studies, which is key for the validity and generalisability of these findings to clinical populations.
- We have examined these issues specifically in patients without cirrhosis and those iatrogenically infected with HCV, and we have examined the impact of extrahepatic conditions and quality of life specifically in HCV-HIV co-infected groups, in order to provide detail on the findings for this group.
- Most importantly, we have tailored the review to the needs of HCV patients themselves in finding out what has a really big impact on their lives, as

opposed to what is easily diagnosable, treatable or pathologically interesting.

Limitations of the evidence

- All of the primary research synthesised in this review was judged to be at moderate or high risk of methodological bias, which could have influenced the results of the studies and thus undermines confidence with regard to our findings in relation to the causal role of HCV in depression, anxiety and pain. Controlling for other confounding factors that potentially explain the relationship between depression, anxiety, pain or quality of life and HCV was not well executed. For example, whether study participants included people who inject drugs (PWID) was not taken into consideration as a confounding factor in many studies.
- The studies we located could only tell us about the association of conditions with HCV infection. Our 'gold standard' study would have been able to tell us about causality and indicate suggested pathways for exploring causality in the future. The National Hepatitis C Register held by Public Health England would provide an ideal sample with which to examine this issue.
- The majority of the included studies were cross-sectional or case-control studies unable to provide information regarding whether or not painful symptoms or conditions occurred prior to infection with hepatitis C. Larger, longer prospective studies with sufficient power and follow-up to determine the association between HCV and pain or painful conditions would help to provide more robust evidence.
- Many of the studies comprised relatively small samples; however, where meta-analysis has been possible, pooled sample sizes allow for a more accurate estimate of the effects of HCV infection upon various outcomes.
- Comparison groups were of questionable equivalence: several studies utilised family members, hospital staff and unknown 'community members' to compare to HCV patients.
- The majority of studies did not examine those who spontaneously cleared HCV yet still experience extrahepatic conditions.
- This set of studies does not tell us anything about the impact of liver disease progression on extrahepatic conditions.
- This set of studies does not examine the impact of interferon treatment on extrahepatic conditions such as depression, although a large proportion of this literature should be readily available for future synthesis, due to our screening methods.
- This set of studies does not examine the effects of antiviral treatment upon patients with chronic hepatitis C infection.

Limitations of our review

- We found that 194 EHCs had been studied as possibly associated with HCV infection. A systematic examination of the literature for all of these possible associations would take several years. Our map of the literature, despite being systematic, can only indicate the kinds of research that have

been conducted and should not be taken as an indication of actual extrahepatic conditions.

- In addition to the conditions examined in the review, patient advocacy groups identified cognitive function and fatigue, in particular, as important conditions impacting upon quality of life. While these are recognised as important topics, we were unable to synthesise these studies within the timelines of the review. We also identified with our map substantial amounts of research on the association between HCV and diabetes mellitus, and pre-diabetic states that may have significant health status burden from a patient's perspective. However, in order to keep to our allotted timeline and resource, we were not able to examine the findings of research examining these conditions. Nonetheless, these studies, and others that potentially examine associations between HCV and extrahepatic conditions have been identified and categorised and are readily available for future synthesis.
- It was only possible for us to briefly assess the National Hepatitis C Register - to understand the prevalence of extrahepatic conditions and the associations with morbidity and mortality in iatrogenically infected persons in the UK. However, this source could be examined in further depth in the future to provide valuable insights into extrahepatic conditions in those with chronic HCV infection.
- Finally, whilst this review's focus on the association of HCV with quality of life and extrahepatic conditions is both an important and essential first step in addressing the problem, it fails to address other important questions, such as which biological or social mechanisms lie behind any associations, the most appropriate intervention approaches to prevent or alleviate the detrimental impacts of HCV and the full implications of any associations for peoples' everyday lives and treatment choices.

Evidence gaps

- To be able to adequately assess causation, longitudinal research with adequate power and sufficient follow-up examining the relationship between HCV and extrahepatic conditions could be undertaken.
- Future research needs to adequately measure, report, adjust for and analyse separately (where appropriate) all data for both sample and comparison groups on important potential confounding factors, including route and duration of infection, liver disease severity, age, gender, education, socio-economic status, and current injection drug and alcohol use. Designs utilising appropriate comparison groups should be employed, matching or adjusting for non-equivalence.
- To understand the relationships between HCV and extrahepatic conditions in iatrogenically infected populations, or people co-infected with HIV and HCV, UK-based research with these people should be conducted.
- There is potential to examine the relationship between extrahepatic conditions and/or quality of life in patients who have cleared HCV

spontaneously as well as those who have undergone treatment, to determine whether the prevalence of extrahepatic conditions is similar.

- To understand whether extrahepatic conditions and quality of life change with liver disease severity, future research reporting and analysing by liver disease severity is warranted.
- A body of research is available on extrahepatic conditions identified as important for quality of life by advocacy group representatives, which would enable syntheses of association between HCV and cognitive function and fatigue.
- A body of research appears to be available for a range of other extrahepatic conditions so that future syntheses could be undertaken as policy need arises. These conditions include diabetes, non-Hodgkins' lymphoma, mixed cryoglobulinaemia, insulin resistance and lichen planus.
- There is a need for a programme of evidence mapping to more fully describe and so identify the full potential of the literature that explores associations between HCV and extrahepatic conditions in general.
- A prospective study of the National Hepatitis C Register should be developed, in order to understand morbidity and mortality related to extrahepatic conditions. Findings from this study could be used to design and conduct a new systematic review on the relevant extrahepatic conditions, using the studies identified in this review.
- To understand a true association between HCV and extrahepatic conditions in iatrogenically infected groups, a longitudinal study should be undertaken comparing the prevalence of extra hepatic complications in patients who acquired HCV from a blood or blood product transfusion against age- and gender-matched groups who were also transfused but did not acquire HCV infection.

SECTION I. Background, results and discussion/conclusions

1. Background

Hepatitis C infection was first described in the medical literature in 1974 but not directly identified as a disease separate from other forms of hepatitis until 1989, when the causal virus was isolated for the first time (Alter et al. 1989). The hepatitis C virus (HCV) is most commonly transmitted when blood from an infected person enters the bloodstream of another. Today, most people infected in Britain acquire the virus through unsterile drug injecting practices. Historically, before an effective blood donor screening test was introduced in the UK in 1991, many people were infected following blood transfusion or treatment with other medical products manufactured from donated human blood. Epidemiological studies estimate that blood transfusion probably resulted in around 23,500 transmissions in England during the 1970s and 1980s (Soldan et al. 2002). Extrapolated to the UK, this figure rises to around 28,000 (Department of Health 2011), and more than 4,500 patients with bleeding disorders were also infected through treatment with HCV-contaminated plasma products. Since 2004, those surviving patients who acquired chronic HCV infection as a result of receiving contaminated blood products have received financial support via the Skipton Fund (Skipton Fund 2013). This provides those patients infected with chronic HCV through NHS blood products with financial remuneration, reimbursement for the cost of prescriptions and free counselling support (House of Commons Debate 2013).

1.1 Natural history of hepatitis C infection

Two disease stages are recognised in HCV infection: acute and chronic. Acute hepatitis occurs within six to eight weeks of infection and may or may not be symptomatic. During this period, viral clearance from the bloodstream may occur (Expert Working Group 2010). In 75% to 85% of those with acute HCV who are not treated, the virus does not clear from the blood, resulting in chronic HCV (Micallef et al. 2006). This is marked by the presence of HCV ribonucleic acid (RNA) for more than six months (Expert Working Group 2010). Cirrhosis develops in around 10% of patients with chronic infection over 15-20 years, and the major direct complications are end-stage liver disease and hepatocellular carcinoma (Kenny-Walsh 1999; Seeff et al. 2001). Patients treated with current therapies (i.e., pegylated interferon and ribavirin) can achieve sustained viral response (SVR) 54–56% of the time (Fried et al. 2002, Manns et al. 2001, Shepherd et al. 2007). However, a stream of new direct-acting anti-HCV agents, expected to be made available in the UK in the near future, should greatly improve treatment outcomes (Public Health England 2013). Current NICE-approved therapy includes the protease inhibitors (National Institute for Health and Care Excellence 2014); currently licensed but not NICE-approved therapies include polymerase and NS5a inhibitors that give SVR in people with HCV genotype 1 (the most common across Europe and North America) of up to 98%.

1.2 Extrahepatic conditions in hepatitis C

In addition to the direct hepatic effects of chronic HCV infection, there is a wide range of published literature on the association of HCV with several conditions occurring outside of the liver ('extrahepatic'), including depression, anxiety and pain, amongst others (Khattab et al. 2010). It has been estimated that around 1-2% of infected individuals will develop any kind of extrahepatic manifestation (Chen and Morgan 2006); many of these experience neurological/psychological conditions (Jacobson et al. 2010). The impact of living with HCV acquired through blood products, and the impact of developing extrahepatic conditions from HCV, is highly variable. In addition, findings from several reviews suggest that people with HCV experience lower quality of life in comparison to the general population (Groessl et al. 2007, Spiegel et al. 2005, Strauss and Teixeira 2006). It is in both of these areas that policy advisers seek evidence, specifically on the causal relationship between HCV and extrahepatic conditions, and on the impact of both of these upon health-related quality of life.

Depression and anxiety in people living with HCV

Depression and anxiety have been implicated as extrahepatic manifestations of HCV; however, the strength of the evidence on which this assertion is based is unclear. Two systematic reviews were located on the topic of depression or anxiety in HCV patients (Jacobson et al. 2010, Ramasubbu et al. 2012); however, these provide an incomplete picture. The review by Jacobson et al. (2010) aimed to assess the clinical and societal implications arising from evidence on the extrahepatic manifestations associated with HCV infection. The authors noted that depression was a predictor for reduced health-related quality of life during treatment for HCV and suggested that the psychological burden of HCV might be to blame. However its findings are questionable: four of the included studies focused on biological mechanisms related to cognitive function or on the relationship of depression to interferon treatment rather than examining the relationship between depression and HCV per se. While two studies did examine this association (Dan et al. 2006, Golden et al. 2005), neither study utilised a comparison group. The review by Ramasubbu et al. (2012) discussed recommendations for the treatment of depression in a variety of chronic conditions, of which HCV was one. The relationship between depression and HCV was only briefly discussed in this review, supported by three references. Of these, two studies were consensus guidelines which did not provide data on the relationship between depression and interferon treatment (Sherman et al. 2007; Strader et al. 2004). The remaining study met our inclusion criteria and was included in our analysis (El Serag et al. 2002).

Primary studies themselves present conflicting findings. For example, Carta et al. (2007) report a significant difference in prevalence of depression between patients with HCV and healthy controls. However a study by Alavian et al. (2007) apparently contradicts this finding by suggesting that in their study, while a statistically significant difference between groups was found, the difference was not clinically significant (i.e., HCV patients scored below the threshold for diagnosis of depression). Trying to pull together such studies is complicated by differences in participants' route of HCV acquisition, previously existing disease, treatment status

and age/years since acquisition; all of which may influence HCV patients' anxiety and/or depression levels. For example, those undergoing treatment with interferon have been shown to experience higher rates of depression (Hubener et al. 2012).

The uncertainty about the associations between depression/anxiety and HCV infection in the research literature, and the priority placed on it by people living with HCV who were consulted, established the need to examine this association in further detail.

Pain and HCV

People living with HCV often report experiencing painful symptoms; these are conditions commonly associated with significant bodily or somatic pain (e.g. fibromyalgia syndrome) (Fontana et al. 2001). A number of painful symptoms are reported in HCV-infected patients. A cross-sectional survey of 1,614 patients with chronic HCV infection finds that painful symptoms such as arthralgia (23%) and myalgia (15%) are among the most commonly observed extrahepatic manifestations (Cacoub et al. 1999). Barkhuizen et al. (1999) report a high prevalence of musculoskeletal pain associated with chronic HCV infection in 239 patients with liver disease: backache (54%) was the most commonly reported pain, followed by morning stiffness (45%), arthralgia (42%), myalgia (38%), neck pain (33%), 'all over' body pain (21%) and joint swelling (20%). They note that musculoskeletal pain is more frequent among patients with isolated HCV infection than among patients with isolated hepatitis B or alcoholic liver disease but do not observe a relationship between musculoskeletal pain and liver disease severity, interferon treatment, or possible route of acquiring HCV (Barkhuizen et al. 1999). Nevertheless, a cross-sectional survey of Irish iatrogenically infected chronic HCV patients (84% female) finds pain reported in the overwhelming majority: 243 of 252 (96%) respondents (McKenna et al. 2009). Similarly, Mohammad et al. (2012) describe a high prevalence (57%) of fibromyalgia syndrome (FS) amongst 185 patients with chronic HCV infection and find that acquisition of HCV through blood transfusion is independently associated with the presence of FS.

Silberbogen et al. (2007) note that whilst pain is frequently associated with HCV infection (irrespective of treatment), the literature on the co-occurrence of HCV and pain is limited and a comprehensive overview of the research in this field is required.

1.3 Quality of life and extrahepatic conditions in people living with HCV

The research evidence points to a multitude of extrahepatic conditions potentially associated with HCV, each with varying impacts on HCV patients' quality of life. For the purposes of this review, health-related quality of life (HRQOL) is defined as a person's subjective assessment of a range of conditions that can affect that person's perception of their state of health (Strauss and Teixeira 2006). This includes symptoms and daily functioning, in addition to medical intervention to assess social and health-related contexts (Groessl et al. 2007, Strauss and Teixeira 2006). HRQOL measures are being used increasingly alongside trials to establish effectiveness and acceptability (Strauss and Teixeira 2006). Such measures add both qualitative and quantitative information about people's opinions and

experiences, thus making them an increasingly useful means of understanding the impacts of disease and of treatment (Groessl et al. 2007).

Only one reliable systematic review was located which examined broad quality of life issues in HCV patients, and none was located which examined quality of life related to extrahepatic conditions. Spiegel and colleagues (2005) examined the relationship between HCV infection and HRQOL. Findings from 32 included studies indicated that HCV-infected individuals experienced lower health-related quality of life scores than healthy controls. Further, health-related quality of life was worse in patients who did not achieve sustained virological response compared to those that did. The authors described large health-related quality of life differences in the neurological, psychological and social domains of HCV-infected patients, yet little variation in health-related quality of life by liver disease severity, suggesting that factors unrelated to biochemical or histological changes in HCV-infected patients, such as the experience of symptoms or stigma, may have a more significant impact on patients' quality of life than disease progression. The authors suggested that such biological outcomes 'may fail to capture the full spectrum of illness related to chronic HCV' (Spiegel et al. 2005, p.796). Importantly, this review is now nine years old. A more recent non-systematic review undertaken by Groessl and colleagues (2007) examined health-related quality of life in HCV infected patients; however its findings should be interpreted with caution, as the authors did not clearly describe their search methods or quality assessment. They noted that health-related quality of life was lower in patients with HCV when compared to healthy populations, was lower in patients with HCV and other conditions or difficult social circumstances, and was lower in HCV patients with increasing levels of disease severity. Psychological disorders such as depression, current injection drug or tobacco use and sexual dissatisfaction were associated with lower HRQOL, suggesting a need to integrate these issues into HCV care. The authors noted that differences in HRQOL were not associated with cognitive impairment scores or cognitive dysfunction; they suggest that relationships seen in previous research were present in the most severe forms of HCV-related liver disease. The authors concluded that fatigue alone may be a better predictor of health-related quality of life in HCV patients, regardless of disease severity.

1.4 The influence of mono- and co-infection

Some evidence suggests that extrahepatic conditions are experienced more severely by those people with HCV who are also co-infected with HIV, in comparison to HCV or HIV alone (Maalouf et al. 2013). However, while there is some literature to contradict this (Halfon et al. 2009; Woitas et al. 2005), these differences may be due to the wide range of conditions under study.

1.5 Summary

In summary, systematic review-level and primary evidence suggests that people with HCV experience a wide variety of extrahepatic conditions and lower health-related quality of life than do healthy controls. However this evidence is now fairly outdated and does not look at health-related quality of life in relation to specific extrahepatic conditions such as depression, anxiety and pain; specific associations

in individuals co-infected with HCV and HIV are unclear. Further, a consistent and comprehensive examination of the influence of age, gender or other mediating factors on the relationship between HCV and extrahepatic conditions has not been undertaken. This incomplete picture of the research evidence suggests the need for a more comprehensive systematic review.

2. Aims and methods

2.1 Aims

The aim of this project, commissioned by the Department of Health in England, was to undertake a systematic review of the literature examining the associations between chronic HCV infection and the development of extrahepatic conditions, and any impact of HCV infection or extrahepatic conditions on health-related quality of life. The purpose of this project was to address identified gaps in current research syntheses and to inform policy and practice on how to address the needs of people in the UK living with chronic HCV. A protocol was created for this review and is freely available upon request (Brunton et al. 2014).

2.2 Research questions

In order to understand the impact on quality of life in HCV-infected patients, we proposed five research questions:

1. In general, how is chronic HCV infection associated with health-related quality of life?
2. Which extrahepatic conditions are associated with chronic HCV infection?
3. What is the strength of the relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?
4. Which groups of people with chronic HCV are affected by extrahepatic conditions? Are there any moderating factors (e.g. age, gender, co-morbidity, iatrogenic acquisition, ethnicity, lifestyle risks) that influence the strength of any relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?
5. Are there any mediating factors (e.g., co-morbidity, socio-economic factors, lifestyle factors) that might explain any observed significant relationship between extrahepatic conditions and health-related quality of life?

2.3 Methods

The research questions were addressed using systematic review methods. Such reviews are well-suited to bring together all of the available research on a topic such as this. They are valuable because they enable us to 'take stock': when based on the entirety of evidence in a given field, they are able to tell us what we do, and do not, know. By applying a consistent, rigorous approach to identifying, selecting and analysing the evidence, systematic review processes reduce the risk of bias inherent in more traditional reviews of the literature. They are efficient because they 'build on' previous research. By employing explicit and reproducible methods to identify included studies, they 'recast' our view of research on a topic, challenging existing assumptions and suggesting new areas for investigation. Systematic reviews facilitate generalisability by looking for knowledge and findings across a body of literature. The careful accounting of methods through each stage of the review ensures that the systematic review is transparent and its results are replicable (Gough et al. 2012, O'Mara-Eves et al. 2013). Systematic review methods

are described briefly here; full details can be found in Chapter 9, in Section II of this report. Using search terms developed by our information scientist, we searched a variety of research sources. These included several electronic databases, specialist websites, sources of published and unpublished literature and key contacts.

The titles and abstracts of all located references were screened according to inclusion and exclusion criteria, and full reports of potentially relevant references were screened again. To be included, studies had to be primary research containing synthesisable data focused on HCV and about either the relationship of HCV to extrahepatic conditions or examining the quality of life in people with HCV, using a control or comparison group. Studies were excluded if they were: not written in English; published prior to 1991; conference abstracts or posters; about treatment or diagnostic tests; about patients with cirrhosis; about compensation; or about biological mechanisms of disease. More detail on these criteria is given in Section 9.3. Studies included at this stage were coded to produce a 'map' of research activity regarding the different extrahepatic conditions examined. HCV advocacy groups and scientific advisers were then consulted regarding the most appropriate conditions to focus on for in-depth synthesis. After consideration of these, further criteria were applied to identify studies for inclusion in this review's syntheses. Details of the synthesis inclusion criteria are provided in Section 9.3.

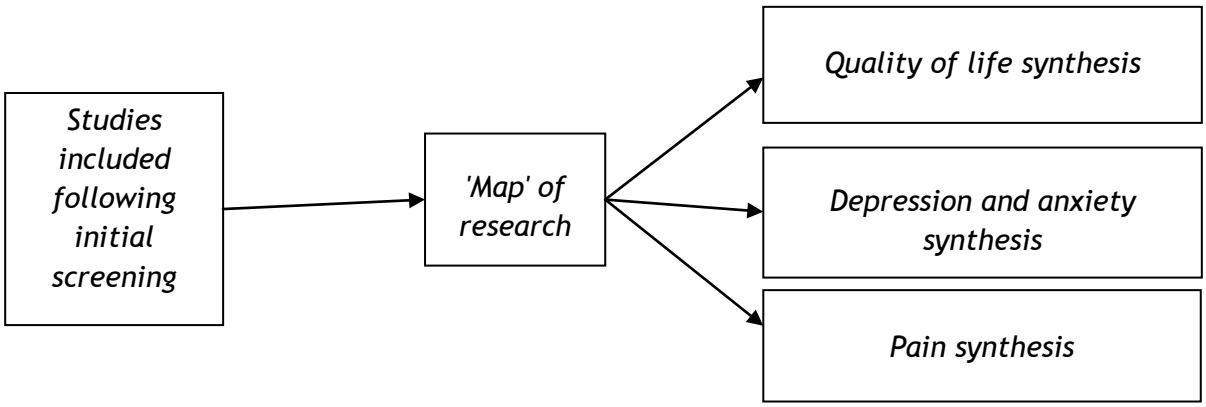
All studies were assessed for methodological quality, using standardised risk of bias assessment tools. Data on the characteristics of studies (e.g. country, sample, comparison group characteristics, control for confounders, measures used, analyses undertaken) and outcome extraction (i.e. effect sizes, p values, confidence intervals) were conducted. Descriptive and statistical analyses were performed on included studies by outcome (i.e. quality of life, extrahepatic condition).

Screening, quality assessment and data extraction were conducted using specialist software EPPI-Reviewer (Thomas et al. 2010). All statistical analyses were undertaken using R software. At least one reviewer assessed included studies at each stage of the review, with findings checked and agreed by a second reviewer and disagreements resolved by a third where necessary.

2.4 How to read this report

We have conducted a two-stage systematic review. First a descriptive 'map' of available research was created by coding and categorising studies according to key variables, e.g. the extrahepatic conditions they examined. The map allowed us to focus subsequent, in-depth analyses of study's findings on research which was identified by advocacy groups and the scientific advisory group as most relevant or appropriate (see Figure 2.1).

Figure 2.1: Two stage systematic review approach



The results for the map of research, extrahepatic conditions and quality of life are presented in subsequent stand-alone chapters. Each of these includes a brief introduction on the specific topic, and the methods, complete findings, discussion, tables and references. Overall discussions and conclusions and recommendations for future research bringing together the findings from each of these chapters follow.

3. Results: mapping the evidence base and identifying priority extrahepatic conditions

3.1 Summary of findings

- A substantial volume of literature was located for this review. This required screening 55,988 studies.
- Consultation with our Scientific Advisory Group identified a need to synthesise studies with the highest morbidity and mortality, but recognised that this focus might differ from that identified by patient groups.
- Patient advocacy groups identified 18 important extrahepatic conditions impacting on quality of life, of which four were identified by all four groups: depression, anxiety, pain and fatigue. We were able within this review to synthesise the findings of the first three of these conditions, along with an examination of the association of chronic HCV infection with quality of life.

3.2 Size of the review task

A total of 55,989 studies of potential relevance were located as a result of the review's searching. The search results, the review's inclusion and exclusion criteria and the process of screening studies are all described in full in Section II of this report.

To inform Advisory Group discussions, the review team's first aim was to produce a systematic map that described key characteristics of the available literature (see Chapter 11 in Section II for a description of the content of this map). This mapping process identified a total of 92 studies that had in some way examined the association between HCV and quality of life. The size of this body of literature was such that it would not be possible to describe and synthesise relevant studies within the time frame of the review project. However, it did help us to prioritise where to focus our efforts with respect to synthesis of quality of life studies.

Initial scoping searches on the extrahepatic conditions (EHCs) associated with HCV, however, had identified 43 conditions. The systematic map confirmed the considerable size of the literature in this area. Research was identified that examined the possible association between HCV and a total of 194 clearly defined extrahepatic conditions. Furthermore, there were potentially additional extrahepatic conditions embedded within these studies, as umbrella terms were often used, such as mental illness or skin conditions.

3.3 Prioritising areas for synthesis

To determine which extrahepatic conditions should be prioritised for this review, we sought information from three sources:

- our Scientific Advisory Group (to determine which conditions had the highest morbidity/mortality and were not yet synthesised)

- representatives from four patient advocacy groups (to determine which conditions had a significant impact on people's quality of life)
- the evidence base of located literature (to determine which topics had the most research and were not yet synthesised).

The information provided via these sources is summarised below (see Chapter 9 for further detail). A brief examination of the National Hepatitis C Register was also conducted.

Consultation with the Scientific Advisory Group

Advisory Group members argued that extrahepatic conditions with the highest morbidity and mortality should be prioritised, but recognised that patient perspectives of morbidity and mortality might differ from those published in the medical literature.

Consultation with advocacy groups

We consulted with representatives from four different advocacy organisations: The Hepatitis C Trust, The Haemophilia Society, Tainted Blood and Contaminated Blood. Advocacy group representatives between them identified 18 extrahepatic conditions that impacted significantly on quality of life. Depression, anxiety, pain and fatigue were the extrahepatic conditions identified as most important by all four groups. Impaired cognition (e.g. 'brain fog', short-term memory loss, insomnia) was identified as important by three of the four advocacy groups.

3.4 Our systematic map of the literature

We were able to use the findings of our systematic map to look at the size and nature of the existing literature examining HCV and extrahepatic conditions and to consider this alongside the advice from our Scientific Advisory Committee and consultations with advocacy groups. It was possible to see that, while individual studies had been conducted that examined associations between three of the areas identified as most important by the advocacy groups (depression, anxiety and pain), there were no recent systematic reviews of this research. Depression and anxiety were most often referred to in tandem by advocacy groups, and evaluated together in the research literature; thus these two topics were considered as one combined topic. Due to time constraints, we were unable to synthesise literature on two other topics identified most frequently by the advocacy groups (fatigue and cognitive function).

3.5 Moving from our systematic map to syntheses

Following the above consultations, additional exclusion criteria were devised to further screen studies included in the map and identify studies to include in syntheses (see Chapter 10 for further detail on the flow of studies through the review).

The application of these criteria to full reports left a total of 71 studies included in the final syntheses: 29 studies of quality of life in people with HCV compared with healthy or normal populations, 22 studies examining the association between HCV

and depression or anxiety, and 26 studies of the association between HCV and pain. Some of these studies examined more than one association. Four examined associations between HCV and both quality of life and depression or anxiety and one studied the association of HCV with depression, anxiety and pain.

4. Results: quality of life and hepatitis C infection

4.1 Summary of findings

- A total of 29 studies examining the relationship between HCV and quality of life met our inclusion criteria.
- Overall, studies were of poor methodological quality; lack of equivalence between HCV and comparison groups was a common weakness.
- Evidence from 22 studies indicates that people with HCV have worse quality of life than 'general' or 'healthy' populations.
- Both the physical and mental domains of quality of life were found to be significantly worse among people with HCV compared to people without HCV, to an extent that would be recognised as clinically relevant.
- Quality of life is reduced in both HCV patients with an iatrogenic infection and with a non-iatrogenic infection when compared to those without HCV.
- Evidence from seven studies indicates that people co-infected with HCV and HIV have worse quality of life than people infected with HIV alone.
- Both physical and mental domains of quality of life were found to be significantly worse among people who were co-infected compared to people with HIV but without HCV.

In this chapter, we examine the association between HCV infection and health-related quality of life (HRQOL) in order to explore whether there is a relationship between having HCV and individuals' perceptions of their state of health. This chapter answers the following questions:

Overarching question:

> *Is chronic HCV infection associated with poorer health-related quality of life?*

Specifically, we answered the following sub-questions relating to various comparisons between different groups with HCV:

1. Do people with chronic HCV infection have poorer health-related quality of life than those from general or healthy populations?
2. Do people who acquired HCV iatrogenically have poorer health-related quality of life than those who acquired HCV through other routes?
3. Do people co-infected with HCV and HIV have a poorer quality of life than those infected with HIV alone?

To answer question 1) we examined evidence from studies comparing quality of life in those with HCV and those without HCV or any other known condition, i.e. healthy populations. This will be referred to as the 'HRQOL general synthesis'. As part of the work for the HRQOL general synthesis, we answered question 2) by conducting a sub-group analysis of data from studies where the HCV participants were exclusively those who had contracted the condition through contaminated

blood products and compared their findings with those from studies which also included HCV patients who had contracted their infection in other ways, such as through unsterile drug injecting practices. This analysis was undertaken to examine whether the overall findings about quality of life among people with HCV were likely to have been confounded or obscured by inclusion of data from participants who currently inject drugs or were previously injection drug users, since drug use may have an impact on quality of life scores.

In relation to question 3), we identified HIV as potentially the most significant mediating factor for the population of interest to the UK Department of Health (DH), i.e. those who acquired HCV infection iatrogenically since the majority of patients iatrogenically infected with HCV will also be infected with HIV (Wilde 2008). Therefore, to answer question 3) we examined evidence from studies comparing quality of life in people with HIV + HCV to those with HIV alone to give an indication of the effect that HCV has over and above the impact of HIV. This will be referred to as the 'HRQOL HIV synthesis'.

Below we briefly describe the methods specific to the quality of life syntheses. The rest of the chapter then reports the findings of each of the quality of life syntheses in turn.

A total of 29 studies examining the relationship between HCV and quality of life met our inclusion criteria.

The HRQOL general synthesis comprises 22 studies which examined the relationship between HCV and quality of life in a general population, three of which examined this relationship exclusively among HCV patients who had contracted the infection through contaminated blood products. Two additional studies that met the criteria for inclusion in the quality of life general synthesis were identified (DiBonaventura et al. 2012, Kramer et al. 2002), but since they examined the same set of data as other included studies (Kramer et al. 2005, Vietri et al. 2013), we excluded them to avoid overstating the precision of the results through double-counting.

The HRQOL HIV synthesis comprises seven studies which compared quality of life outcomes among co-infected HIV/HCV patients to patients with HIV only.

Below we present the findings for each of the two quality of life syntheses in turn. For each synthesis we present an overview of the characteristics of the included studies followed by an analysis of the studies' findings; the findings sections comprise the details of a statistical meta-analysis followed by a narrative assessment of the evidence. Tables A4.1 and A4.2 in Appendix 4 provide full details of the study characteristics and findings for each of the 29 studies in the two quality of life syntheses.

4.2 Description of studies: HQROL general synthesis

Table A4.1 in Appendix 4 presents the characteristics of each of the 22 studies; below is a narrative overview of the nature of the set of studies comparing quality of life in those with HCV to those without HCV.

Quality and relevance of the included studies

Overall, the quality and relevance of the 22 studies was poor. No studies were judged as having a low risk of bias, and just two were judged to have a moderate risk of bias (Heeren et al. 2013, Lowry et al. 2010); the remainder were judged as being at high risk of bias. Details of the appraisal of each of the 22 studies can be found in Table A3.1 in Appendix 3.

One common weakness was that studies did not employ an appropriate control or comparison group or take steps to minimise confounding bias. In most studies, HCV and control groups were matched or at least equivalent in terms of the age and gender of participants; however, in the majority of studies, the proportions of PWID either differed between HCV patients and controls or were not reported. Only studies which controlled for PWID in their samples (in addition to other demographic variables) were judged as having an appropriate control or comparison group (n=4); two studies were matched for age and gender and focused exclusively on HCV participants who had contracted the condition iatrogenically (Heeren et al. 2013, Lowry et al. 2010) and two studies were matched for age and gender and excluded people who were current injection drug users from their sample (Kramer et al. 2005, Pojoga et al. 2006).

Another common weakness of the included studies was that few reported sufficient information to suggest that the sample was actually representative of the target population (n=7). Three described the use of a random or stratified approach to the selection of participants (DiBonaventura et al. 2010, Kwan et al. 2008, Vietri et al. 2013); a further four described a high participation rate (>90%) among patients eligible for the study (Foster et al. 1998, McHutchison et al. 2001, Svirtlih et al. 2008, Teixeira et al. 2006).

In relation to the validity of independent and dependent variable measurement, the studies were largely sound. All studies employed the widely used and validated SF36 to measure quality of life and just three studies were found not to have employed a clinical measure of HCV status (i.e. they asked participants to self-report their HCV status) (DiBonaventura et al. 2010, El Khoury et al. 2012, Vietri et al. 2013).

Just seven studies were assessed as being highly relevant to the scope of this review since they focused on HCV populations of particular interest: five examined quality of life among those who had acquired HCV iatrogenically (Foster et al. 1998, Heeren et al. 2013, Hollander et al. 2006, Kramer et al. 2005, Lowry et al. 2010), one included only a minority of participants who had acquired HCV non-iatrogenically (Pattullo et al. 2011) and one excluded current injection drug users (Pojoga et al. 2006). Although these studies were more relevant than others with regard to the HCV populations examined, there were still limitations with regard to their relevance; only one of the 22 included studies was conducted in the UK and two of the three studies which examined quality of life in populations with exclusively iatrogenic acquisition were conducted with very small all-female samples.

Country of origin, study setting, comparison groups

Six of the included studies were undertaken in the USA, two studies were undertaken in Brazil and one study was undertaken in each of the following countries: Austria, Canada, Germany, Greece, Iran, Ireland, Romania, Serbia, Spain, Sweden, Taiwan and the United Kingdom. Two studies comprised international samples, one from European countries only and one from the US and Canada as well as European countries.

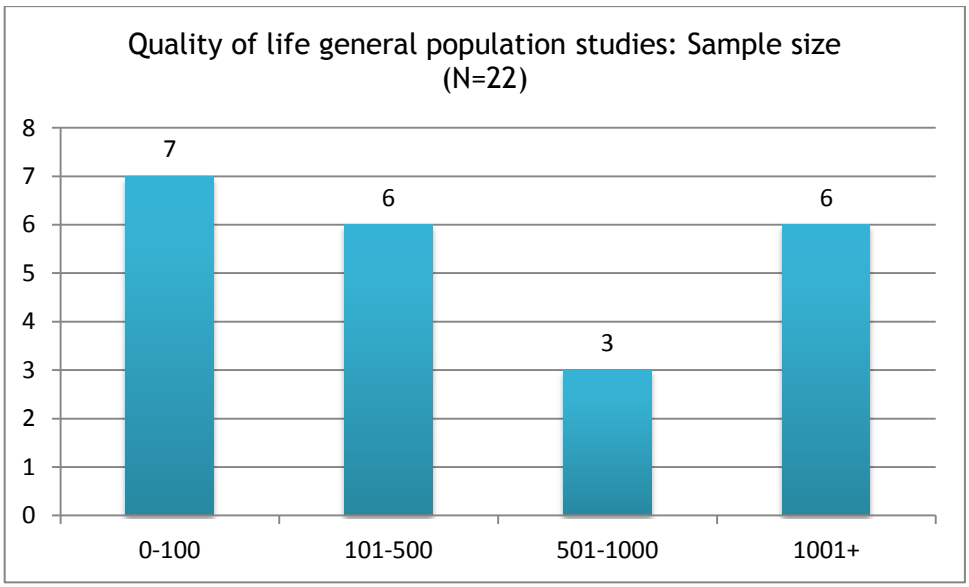
Study samples were drawn from a range of settings, most commonly drawn from hospital-based specialist HCV clinics (n=9). In six studies, the samples were those participating in a trial of HCV treatments such as interferon (Bayliss et al. 1998, Bonkovsky et al. 1999, McHutchison et al. 2001, Pojoga et al. 2006, Sinakos et al. 2010, Ware et al. 1999). Two studies drew their samples from blood donation clinics (Strauss et al. 2013, Teixeira et al. 2006) and one from an HCV support group (Heeren et al. 2013). The remaining four studies drew their sample from respondents to national or international health surveys; they compared respondents reporting a diagnosis of HCV to those not reporting an HCV diagnosis (DiBonaventura et al. 2010, El Khoury et al. 2012, Kwan et al. 2008, Vietri et al. 2013). As can be seen from Table A4.1 in Appendix 4, the control groups were either drawn from the same source as the HCV participants or comprised matched population norms.

Study design, sample size

All studies included in the analysis were of cross-sectional design; no studies of longitudinal design were located (i.e., measuring depression or anxiety at more than one time point). Sample sizes ranged from 29 to 8,591 participants.

The two studies with the smallest samples (Heeren et al. 2013, n=39, Lowry et al. 2010, n=29) both focused exclusively on iatrogenic populations (i.e. those who had contracted the virus through contaminated blood products). The third study focusing on an exclusively iatrogenic population (Hollander et al. 2006) comprised the largest sample of all included studies (n=8,951) but the vast majority of its participants were accounted for by its control group of n=8,930). Indeed, in most of the largest samples (n=1,001+) the control group was far larger than the HCV group; in half of the included studies (n=11) the HCV group comprised 100 participants or less. After Hollander et al. (2006), the next two largest studies did, however, include relatively large numbers of HCV participants: the sample from DiBonaventura et al. (2010) included 695 HCV participants and 695 controls, and McHutchison et al. (2001) included 905 participants in each group (HCV and control). Figure 4.1 illustrates the distribution of samples sizes across studies.

Figure 4.1: Distribution of sample size across HRQOL general population studies (n=22)



Participant demographics

The mean age of samples ranged from 36 to 60 years. Two studies included female participants only (Heeren et al. 2013, Lowry et al. 2010). However, of the remaining 20 studies, 16 included a majority of male participants; the percentage of male participants ranged from 40 to 99.

Route of HCV acquisition

Three of the studies examined quality of life exclusively or predominantly in populations who had acquired HCV iatrogenically (Heeren et al. 2013, Hollander et al. 2006, Lowry et al. 2010). Eight of the remaining 19 studies indicated that they examined mixed populations with regard to HCV acquisition route, the vast majority indicating that only a minority of participants had acquired HCV iatrogenically. The proportion of those who had acquired the infection through contaminated blood products was specified in six studies (Ashrafi et al. 2012, 19%, Bayliss et al. 1998, 36%, Bonkovsky et al. 1999, 24%, Cordoba et al. 2003, 43%, Kramer et al. 2005, 44%, Ware et al. 1999, 27%); a further two studies indicated the proportion of participants who had previous history of injection drug use (Pattulo et al. 2011 18%, Sinakos et al. 2010 63%). Eleven studies provided no information on how the HCV participants had acquired their infection (DiBonaventura et al. 2010, El Khoury et al. 2012, Foster et al. 1998, Kang et al. 2005, Kwan et al. 2008, McHutchison et al. 2001, Pojoga et al. 2006, Strauss et al. 2013, Svirtlih et al. 2008, Teixeira et al. 2006, Vietri et al. 2013).

Liver disease severity

Studies varied in the extent to which they excluded or accounted for patients with cirrhosis. Six studies excluded patients with cirrhosis (Ashrafi et al. 2012, Cordoba et al. 2003, Foster et al. 1998, Heeren et al. 2013, Pattullo et al. 2011, Pojoga et al. 2006), and a further study described the included HCV population as having

'mild chronic hepatitis' (Lowry et al. 2010). Seven studies reported that less than 25% of the HCV participants in their studies had cirrhosis (Bayliss et al. 1998, Bonkovsky et al. 1999, El Khoury et al. 2012, Kramer et al. 2005, Kwan et al. 2008, Svirtlih et al. 2008, Ware et al. 1999). Sinakos et al. (2010) reported that the fibrosis stage of 63% of HCV participants was <2. Six studies did not report the condition of the liver of participants (DiBonaventura et al. 2010, Kang et al. 2005, McHutchison et al. 2001, Strauss et al. 2013, Teixeira et al. 2006, Vietri et al. 2013).

People who inject drugs

As described above, three of the included studies focused exclusively on samples who had acquired the infection iatrogenically; for these studies, it is assumed that none of the participants were PWID. Nine of the remaining 19 studies' authors described the previous and/or current use among participants who were PWID. Four studies described the proportion of current users: in three studies this was 0% of participants and in the fourth it was 21%. All nine studies described the proportion of participants with a previous history of drug use, which ranged from 0% to two thirds (64%); most reported proportions below half (n=6). Table 4.1 provides details of the nine studies with such details.

Table 4.1: Details of studies describing proportions of PWID (n=9)

Study	Current users	Previous history
Ashrafi et al. (2012)	21%	51%
Bonkovsky et al. (1999)	-	43%
Cordoba et al. (2003)	-	2%
Foster et al. (1998)	0%	50%
Kramer et al. (2005)	0%	24%
Pattullo et al. (2011)	-	18%
Pojoga et al. (2006)	-	0%
Sinakos et al. (2010)	-	64%
Teixeira et al. (2006)	0%	19%

Treatment for HCV

Ten of the 22 studies specifically included HCV patients who were treatment naïve (i.e. they had not undergone any form of antiviral therapy) (Bayliss et al. 1998, Bonkovsky et al. 1999, El Khoury et al. 2012, Kramer et al. 2005, Lowry et al. 2010, Pattullo et al. 2011, Sinakos et al. 2010, Strauss et al. 2013, Svirtlih et al. 2008, Teixeira et al. 2006). Five studies were explicit that none of the participants in

their studies were currently undergoing therapy (Foster et al. 1998, Heeren et al. 2014, Kwan et al. 2008, Pojoga et al. 2006, Ware et al. 1999). Three studies did not report the treatment status of participants (Cordoba et al. 2003, DiBonaventura et al. 2010, McHutchison et al. 2001). All other studies (n=4) reported that some HCV participants had recently undergone or were currently in therapy (Ashrafi et al. 2012, Hollander et al. 2006, Kang et al. 2005, Vietri et al. 2013).

Exclusions

The majority of the 22 studies excluded HCV participants with co-morbidities; just three studies did not exclude participants on this basis (Kang et al. 2005, Kwan et al. 2008, McHutchison et al. 2001). Typically, studies excluded participants with HBV (n=10) or HIV (n=12). A total of 12 studies excluded participants with a range of other health conditions, including psychiatric illness and physical conditions such as diabetes (see Table A4.1 in Appendix 4 for details). Comparison or control groups were typically subject to the same exclusion criteria.

HCV measures

The vast majority of studies confirmed HCV infection: 16 by RNA polymerase chain reaction testing and three by liver biopsy. The remaining three studies were all surveys and participants were asked to report whether they had been diagnosed by a physician with having an HCV infection (DiBonaventura et al. 2010; El Khoury et al. 2012, Vietri et al. 2013); authors in each of these studies acknowledged that the lack of verification of the HCV diagnosis was a potential weakness in their research design.

Quality of life measures

All 22 used standardised short form health surveys to measure quality of life, either the SF36 (n=17) or the even shorter SF12 (n=5). Both use the same eight individual outcomes scales to evaluate quality of life; the eight individual scales encompass physical function, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health. Common to both the SF12 and SF36 are summary scales which collapse findings into a physical component summary (PCS) and a mental component summary (MCS). One study (Bayliss et al. 1998) augmented evidence on quality of life from the SF36 measures with measures from the Medical Outcomes Study (MOS) scale, which the authors hypothesised would assess some effects of HCV not captured by the SF-36 (sleep somnolence and health distress), or to amplify the measurement of the sub-domains of the SF-36 scales (positive wellbeing, incorporated in the SF-36 mental health scale). Table 4.2 illustrates which measure was used (SF12 or SF36) and which scales were reported (individual and/or summary scales). Henceforth, all short-form outcomes, from either the SF36 or SF12, will be referred to in the narrative as SF36 outcomes.

Table 4.2: Quality of life measures used (n=22)

Study	Measure	Individual scales	Summary scales (MCS/PCS)
Ashrafi et al. (2012)	SF12		✓
Bayliss et al. (1998)	SF36	✓	
Bonkovsky et al. (1999)	SF36	✓	
Cordoba et al. (2003)	SF36	✓	✓
DiBonaventura et al. (2010)	SF12	✓	✓
El Khoury et al. (2012)	SF12		✓
Foster et al. (1998)	SF36	✓	
Heeren et al. (2013)*	SF36		✓
Hollander et al. (2006)	SF36	✓	✓
Kang et al. (2005)	SF36	✓	
Kramer et al. (2005)	SF36	✓	
Kwan et al. (2008)*	SF36		✓
Lowry et al. (2010)	SF36	✓	
McHutchison et al. (2001)	SF36	✓	
Pattullo et al. (2011)	SF36		✓
Pojoga et al. (2006)	SF36	✓	
Sinakos et al. (2010)	SF36	✓	
Strauss et al. (2013)	SF36	✓	✓
Svirtlih et al. (2008)	SF12		✓
Teixeira et al. (2006)	SF36	✓	
Vietri et al. (2013)	SF12		✓
Ware et al. (1999)	SF36	✓	

*Data not suitable for meta-analysis

4.3 Findings: quality of life in people with HCV compared to 'general' or 'healthy populations'

A number of statistical meta-analyses could be performed to examine the relationship between HCV status and quality of life outcomes. One examined the impact of HCV status on the physical component summary (PCS) and one on the mental component summary (MCS); a third explored mean differences in scores between HCV and general populations for the eight SF36 individual subscales and a fourth explored individual component scores exclusively among participants who had acquired HCV iatrogenically. All scales for individual subscales and summary scores are based on a range of 0-100, with a lower score indicating a greater level of impairment. A mean difference of between three and five points on any scale is considered to be the minimum level of importance or of clinically significant difference, i.e., it would indicate a clearly perceivable difference in the quality of life between those with HCV and general populations (Samsa et al. 1999, Spiegel et al. 2005).

Figure 4.2 shows the meta-analysis for the SF36 PCS comparing people with HCV to 'general' or 'healthy' populations. It shows that, in relation to people's perception of their own *physical* health, those with HCV had worse scores: on average people with HCV have a PCS score 5.5 points lower than people without HCV. Heterogeneity was substantial (I^2 =79%), suggesting differences in the effect of HCV on quality of life across studies and populations. There was borderline evidence of funnel plot asymmetry (Egger's test p-value 0.098), suggesting a possibility of preferential publication where people with HCV were found to have had worse PCS scores. The meta-analysis included data from nine of eleven studies providing data on PCS outcomes (see Table 4.2 for details); the remaining two studies, though not amenable to meta-analysis, provided corroborative findings. The Heeren et al. (2013) study gave very discordant results (mean difference (MD) = 37) and the study by Kwan et al. (2008) did not report standard differences for adjusted figures though the authors did note that after adjusting for demographic variables and co-morbid illnesses, HCV patients reported a trend toward a slightly impaired PCS score (MD p <0.07) compared to participants without HCV.

Figure 4.2: Mean difference in SF36 PCS scores between people with HCV and those without HCV (n=9 studies)

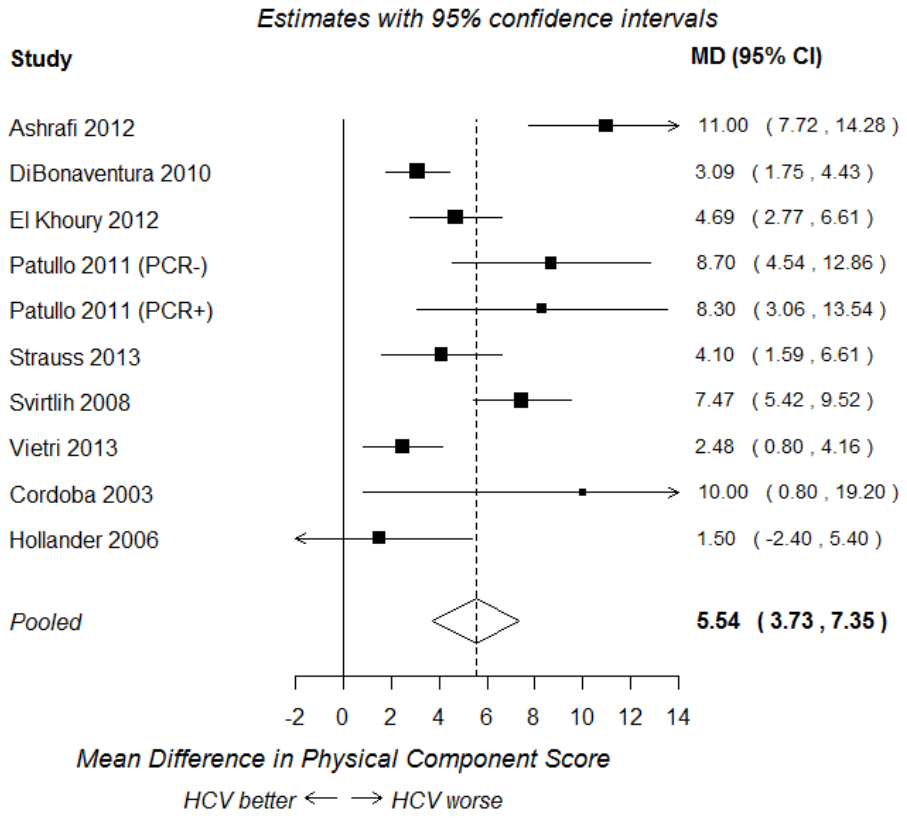


Figure 4.3 shows the meta-analysis for SF36 MCS, i.e., comparing people with HCV to those without HCV regarding their perception of their mental health. The results were similar to the physical component: people with HCV were found to have, on average, an MCS score 3.8 points lower than people without HCV. The mean difference was slightly lower than for the PCS and should perhaps be regarded as of borderline clinical significance (Samsa et al. 1999; Spiegel et al. 2005). Heterogeneity was substantial (I^2 = 70%). There was borderline evidence of funnel plot asymmetry (Egger's test p-value 0.101). As with the PCS findings, the meta-analytic findings on MCS were corroborated by an additional two studies that reported MCS figures but were not amenable to meta-analysis (Heeren et al. 2013, Kwan et al. 2008). In fact, with regard to MCS, the Kwan study reported that between-group differences adjusted for demographic variables and co-morbid illnesses were statistically significant (p. < .001).

Figure 4.3: Mean difference in SF36 MCS scores between people with HCV and those without HCV (n=9 studies)

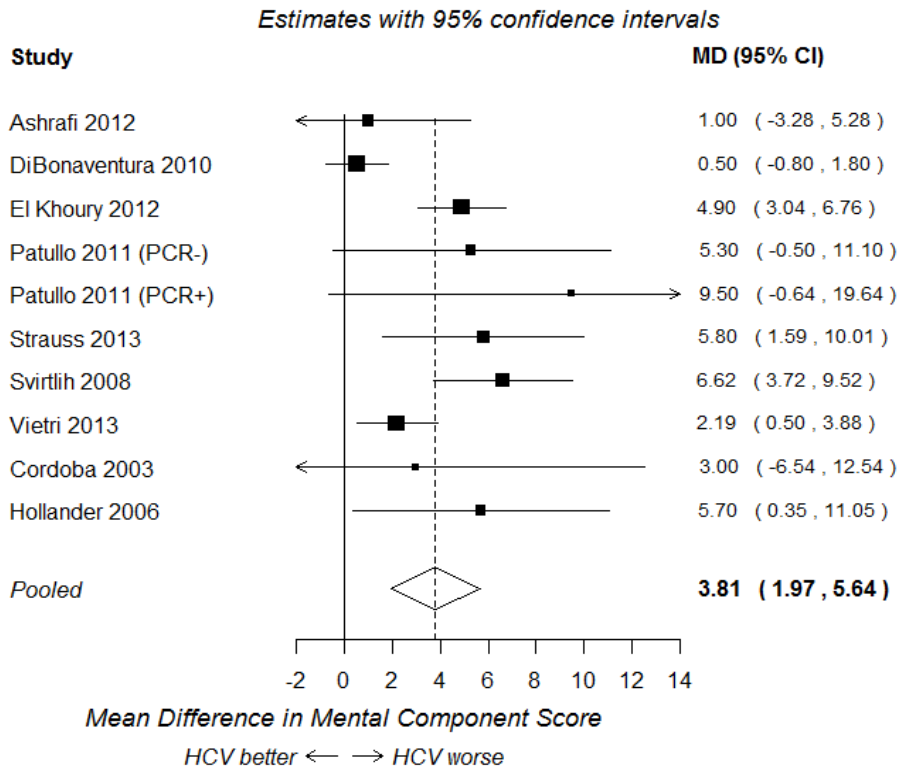
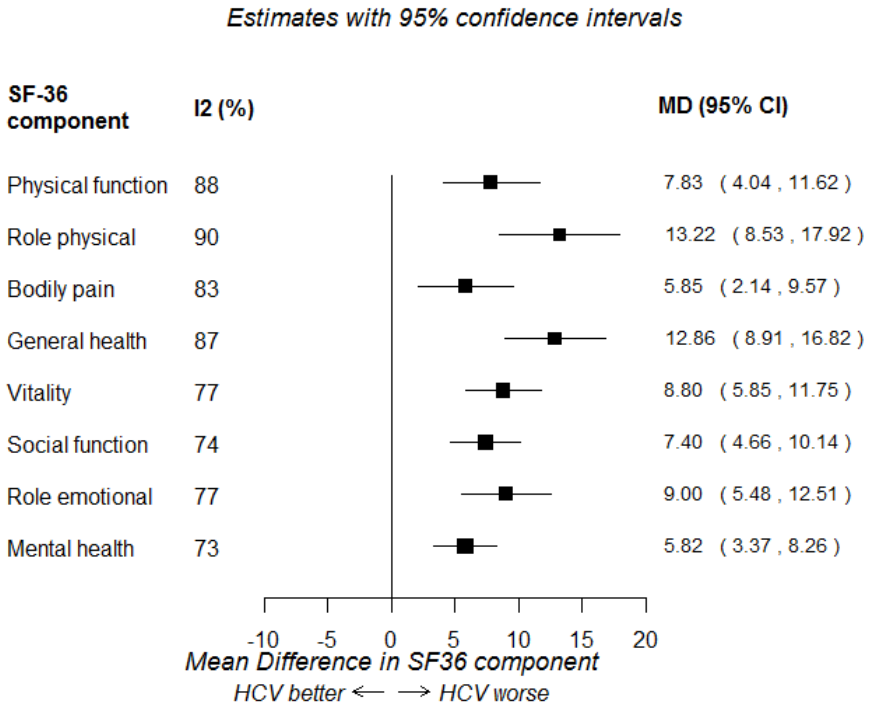


Figure 4.4 shows the results of meta-analyses for all eight components of the SF36 score (13 studies). All show statistically and clinically significant evidence that scores are worse in people with HCV, ranging from around 6 points worse for mental health, to around 13 points worse for physical role and general health. The heterogeneity was high in all analyses. There was no statistically convincing evidence of any relationship between the impact of HCV on PCS or MCS scores and either age, gender or injection drug use (data not shown). A further two studies provided data on the eight SF36 components but provided insufficient information to enable inclusion in the meta-analysis (Bonkovsky et al. 1999, McHutchison et al. 2001); findings from both studies corroborated the evidence of reduced scores among HCV patients compared to general populations. Bonkovsky et al. (1999) reported significantly lower scores among HCV patients compared to 'well norms' on all eight components and McHutchison et al. 2001 reported reduced scores for HCV patients compared to general population scores for all eight scales, five of which were found to be significantly lower.

Figure 4.4: Mean difference in SF36 components between people with HCV and those without HCV (n=13 studies)



Iatrogenic infection in people with HCV compared to 'general' or 'healthy' populations

We now consider the studies where all those with HCV had acquired it iatrogenically (Hollander et al. 2006, Lowry et al. 2010). The study by Heeren et al. (2013) was not considered because of its discordant data, as described above.

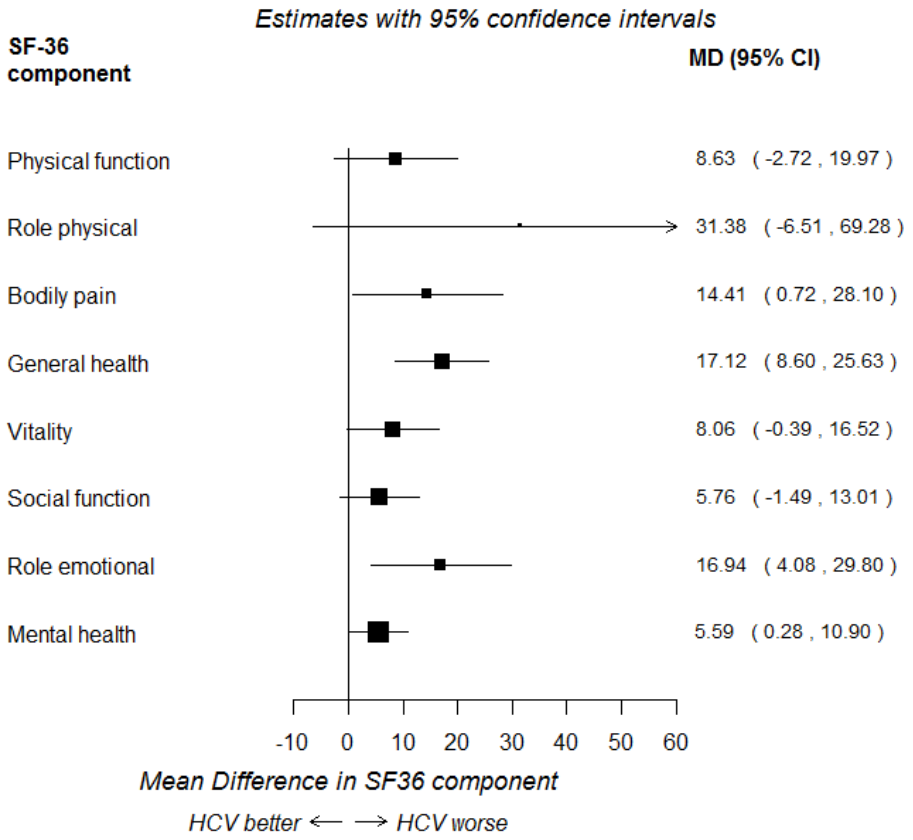
Only Hollander (2006) reported PCS and MCS scores. From Figures 4.1 and 4.2, it can be seen that the PCS and MCS scores in this study are broadly consistent with the other studies where there was some non-iatrogenic infection, although the mean difference in PCS is lower in the participants in the study by Hollander et al. than for most other studies.

Figure 4.5 shows the meta-analysis of SF36 components in both studies. It is difficult to draw conclusions from only two studies, but the available evidence indicates that quality of life is reduced in both HCV patients with an iatrogenic infection and HCV patients with a non-iatrogenic infection when compared to those without HCV, and the deficit appears to be of a similar magnitude.

Notwithstanding the discordant results of the Heeren et al. (2013) study (which also showed a deficit), two other studies also provided some corroborative evidence regarding the negative impact of iatrogenically acquired HCV on quality of life, although they provided insufficient data to contribute to the meta-analysis (Foster et al. 1998, Kramer et al. 2005). Kramer et al. (2005) found no difference between previous injection drug users and other patients with respect to quality of

life and Foster et al. (1998) found that patients who had never used drugs had significant reduction in quality-of-life scores for seven of the eight scales compared with healthy controls.

Figure 4.5: Mean difference in SF36 component scores in two studies of iatrogenic infection (n=2 studies)



However, two studies also provided some evidence that the route of acquisition may have some impact on quality of life outcomes for people with HCV (Foster et al. 1998, Hollander et al. 2006). Foster et al. (1998) found that patients with chronic HCV who had used injection drugs in the past had greater impairment in quality-of-life scores than those who had never used drugs. Similarly, Hollander et al. (2006) found that quality of life among PWIDs was 'much worse' than that found in patients who had acquired their infection iatrogenically.

4.4 Description of included studies: HRQOL HCV-HIV synthesis

Seven studies comparing quality of life in those co-infected with HIV and HCV to those with HIV only met all relevant inclusion criteria (Briongos Figuero et al. 2011, Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Rourke et al. 2011, Tillmann et al. 2006, Tsui et al. 2007). Table A4.2 in Appendix 4 provides an overview of the characteristics of these seven studies.

Quality and relevance of the included studies

The quality of the seven studies was relatively poor overall. None described an appropriate comparison group, i.e., with comparable socio-demographic characteristics such as age, gender and rates of substance use. None of the seven studies used matching or other methods to make sample and comparison groups comparable. Two studies limited their description of demographics to all study participants as a whole and did not report data separately for co-infected patients and those with HIV alone (Briongos Figuero et al. 2011, Tillmann et al. 2006). All five studies that described both study groups separately identified statistically significant differences between groups in the proportion of PWIDs (who were therefore likely to have been infected through this route) (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005), or in terms of current injection drug use (Tsui et al. 2007) or 'substance use' (Rourke et al. 2011).

Four studies made attempts to account for potential confounding (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Tsui et al. 2007); and all four used statistical methods (regression) to control for relevant confounders.

Only three studies (Briongos Figuero et al. 2011, Kanwal et al. 2005, Rourke et al. 2011) reported sufficient information to suggest that their sample was likely to be representative of their population of interest (external validity). While all studies used a validated tool to measure quality of life, only six described appropriate methods for measuring HCV infection. One study indicated using self-report methods (Rourke et al. 2011).

The relevance of studies to the population of interest in our review was relatively low. The route of HCV acquisition was either primarily injection drug use rather than iatrogenic infection (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Rourke et al. 2011, Tsui et al. 2007), or was not reported separately for the co-infected group (Briongos Figuero et al. 2011, Tillmann et al. 2006).

Because of a lack of an appropriate comparison group accompanied by limitations in sampling and measurement, all but one of the seven studies (Kanwal et al. 2005) were judged to be at a high risk of bias.

Table A3.2 in Appendix 3 provides details of the quality judgements for each study.

Country of origin, study setting, comparison groups

Three studies were conducted in the USA, two in Canada, one in Spain and one in Germany.

Studies were undertaken in a range of settings. Hospital-based specialist clinics were the settings for two of the seven included studies (Briongos Figuero et al. 2011; Fleming et al. 2004); four involved participants enrolled in cohort studies sampling from multiple care settings: HIV-care across the whole of the USA (Kanwal et al. 2005); HIV care across a region of Canada (Gillis et al. 2013, Rourke et al. 2011), and care for people with HIV in San Francisco who were homeless or in marginal housing (Tsui et al. 2007). In one study, recruitment methods were not reported, but researchers appeared to have sampled from existing patient records

(Tillmann et al. 2006). In all studies, the comparison group was recruited from the same setting and consisted of those people identified as not being HCV positive.

Study design, sample size

All studies included in the analysis were of cross-sectional design. No studies of longitudinal design were located (i.e. employing measurement of depression or anxiety at more than one time point).

Two of the studies used data from over a thousand participants. Gillis et al. 2013 studied 1,095 participants in the Ontario HIV Treatment Network Cohort Study, conducted across several separate care sites in Canada. The study by Kanwal et al. (2005) involved 1,772 participants in the US HIV Cost and Services Utilization Study (HCSUS). The remaining five studies had between 100 and 500 participants (Briongos Figuero et al. 2011, Fleming et al. 2004, Rourke et al. 2011, Tillmann et al. 2006, Tsui et al. 2007).

Participant demographics

Five studies provided data that described both study groups separately (the group of participants co-infected with HIV and HCV and the group with HIV but without HCV) (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Rourke et al. 2011, Tsui et al. 2007). In these studies, the mean age of co-infected participants ranged from 40 to 46. These studies all involved more men than women, with the proportion of men who were co-infected ranging from 72% to 83%. Only two of the seven studies excluded participants because of additional co-morbidities. Both excluded participants with HBV (Gillis et al. 2013, Kanwal et al. 2005). The remainder did not report HBV prevalence. Comparison or control groups were typically subject to the same exclusion criteria.

Route of HCV acquisition

None of the studies examined quality of life exclusively or predominantly in populations who had acquired HCV iatrogenically. All studies indicated that they examined mixed populations with regard to HCV acquisition route. Three studies specified the proportion of co-infected participants who had injection drug use as a risk factor for viral infection (Fleming et al. 2004, 89%, Gillis et al. 2013, 41%, Kanwal et al. 2005, 49%) and two reported the prevalence amongst co-infected participants of substance use in last 12 months (Rourke et al. 2011, 71%) and current injection drug use (Tsui et al. 2007, 45%). A further two studies presented the proportion of PWID only for study participants as a whole (Briongos Figuero et al. 2011, 84%, Tillmann et al. 2006, 14%).

Treatment for HCV

Only one of these seven studies reported the number of participants taking HCV medication (Gillis et al. 2013 5%). The proportion of co-infected participants currently on antiretroviral medication (ART) was reported in five studies, with prevalence ranging from 16% (Tsui et al. 2007) to 75% and upwards (Briongos Figuero et al. 2011, 84%, Fleming et al. 2004, 75%, Gillis et al. 2013, 85%, Kanwal et al. 2005, 85%). The remaining two studies reported the proportion of

participants who had ever taken ART (Rourke et al. 2011, 74%) or did not describe participants' history of drug treatment at all (Tillmann et al. 2006).

Liver disease severity

None of the seven studies described the liver status of participants.

HCV measures

All but one of the studies (Tillmann et al. 2006) indicated that HCV infection was chronic in nature. Only one study confirmed current HCV infection by RNA polymerase chain reaction testing (Tsui et al. 2007), the rest obtained information about HCV status from existing medical notes (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Tillmann et al. 2006), or through self-report only (Briongos Figuero et al. 2011, Rourke et al. 2011). One study included only those patients who had a record of detectable HCV RNA (Fleming et al. 2004).

Quality of life measures

Several measures were used to measure quality of life in this set of studies, as shown in Table 4.3.

Table 4.3: Quality of life measures used (n=7)

Study	**MOS-HIV**	**SF-36 v.2**	**Hepatitis Quality of Life questionnaire**	**HCSUS**	**HIV-SELT**
Briongos Figuero et al. (2011)					
Fleming et al. (2004)			✓		
Gillis et al. (2013)		✓			
Kanwal et al. (2005)				✓	
Rourke et al. (2011)					
Tillmann et al. (2006)					✓
Tsui et al. (2007)		✓			

The MOS-HIV and the SF-36 v. 2 were each used in two studies. These scales, and the Hepatitis Quality of Life questionnaire and the HCSUS measure used in of a further one study each used a similar set of eight domains, and could be used to create two summary scores for mental and physical quality of life. These were judged to be sufficiently similar for use in meta-analysis. The remaining study used the HIV-SELT (Tillmann et al. 2006).

4.5 Findings: quality of life in people co-infected with HCV and HIV compared to those with HIV only

There were seven studies in which all participants were co-infected with HIV, and compared HIV with HCV to HIV infection alone. Five studies provided data for meta-analysis, in the form of unadjusted means, for the two study groups. The other two studies either provided no data in the form of means (Briongos Figuero et al. 2011), or had used a quality of life measure that was too dissimilar to the SF-36 (Tillmann et al. 2006).

Figures 4.6 and 4.7 show the forest plots for the SF36 PCS and MCS mean differences respectively in the five studies; Figure 4.8 shows the forest plot for SF36 components (2 studies). The analyses indicate that people co-infected with HIV and HCV have worse quality of life than those with HIV alone.

In all three analyses, the differences between participants with and without HCV are rather smaller than those observed in the quality of life general synthesis reported above. This suggests that the extra impact of HCV infection is modest (above and beyond the large impact already made by HIV infection). In most cases, it may be smaller than that considered clinically meaningful. There was some heterogeneity across studies, but less than for the studies without HIV (general population synthesis) (PCS: I^2 = 56%, MCS, I^2 = 61%). As there were only five studies, no meta-regression analyses to assess potential causes of heterogeneity were performed.

Four of the studies had conducted regression analyses with the aim of accounting for potentially confounding variables (Fleming et al. 2004, Gillis et al. 2013, Kanwal et al. 2005, Tsui et al. 2007). All adjusted not only for age and sex, when differences were found between groups, but also for PWID, or perceived risk factors for HIV, and for one or more co-morbidities. Of these, two found that, after adjustment, co-infection with HCV was associated with a lower PCS, but no longer associated with a lower MCS (Gillis et al. 2013, Tsui et al. 2007). The other two found no association with either scale, either before or after adjustment (Fleming et al. 2004, Kanwal et al. 2005).

The two studies not amenable to meta-analysis had also conducted regression analyses but were judged to be at high risk of bias since neither had demonstrated the equivalence of their study groups or had considered PWID as a potentially confounding variable. Nonetheless, their findings to some extent corroborated the meta-analytic findings: adjusted figures in Briongos Figuero et al. (2011) suggested that people with HIV only were less likely to have poor mental health scores, and adjusted figures in Tillmann et al. (2006) showed that those with HCV in addition to HIV had impaired quality of life outcomes compared to those with HIV alone. The study by Rourke et al. (2011) did not include regression analyses.

Figure 4.6: Mean difference in SF36 PCS scores in studies with HIV co-infection

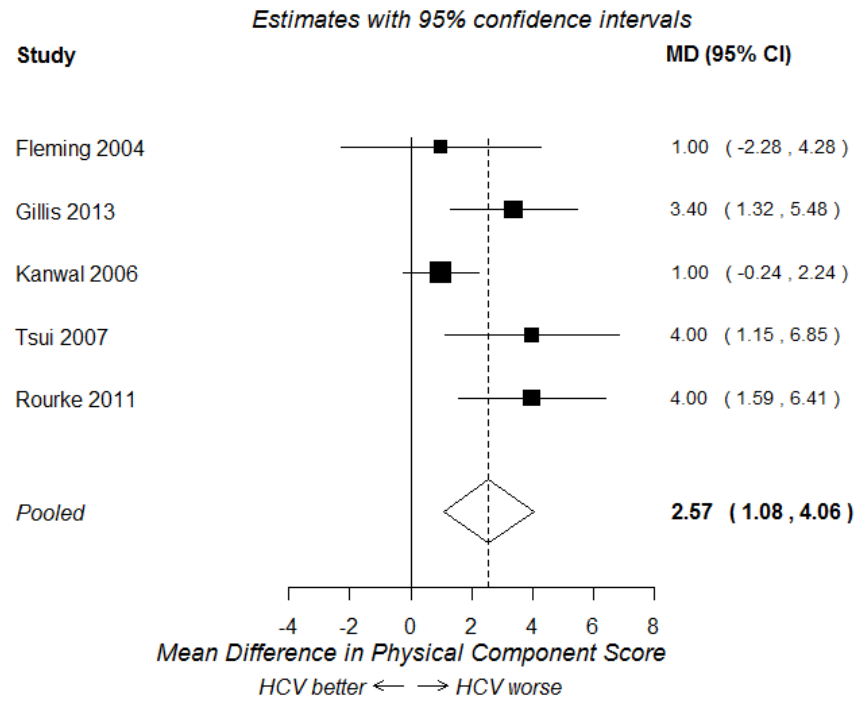


Figure 4.7: Mean difference in SF36 MCS scores in studies with HIV co-infection

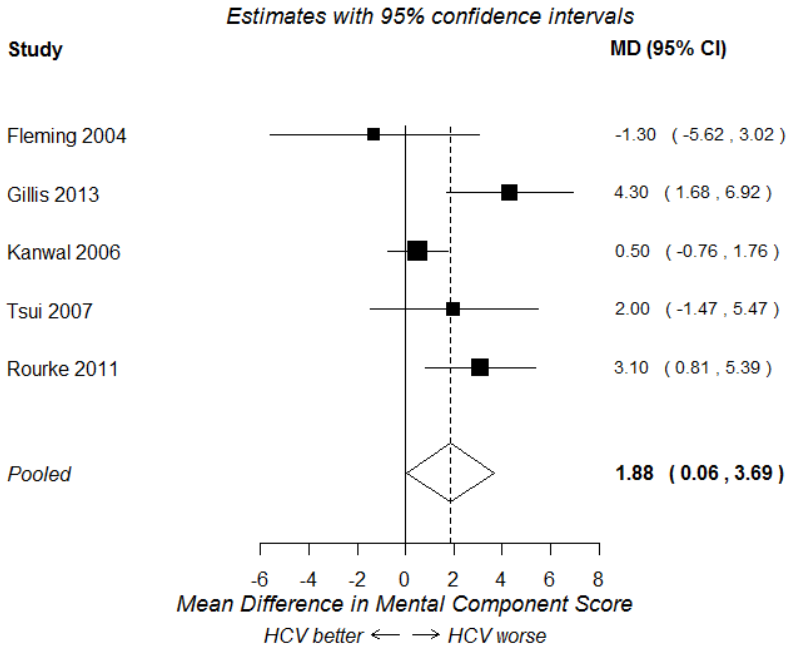
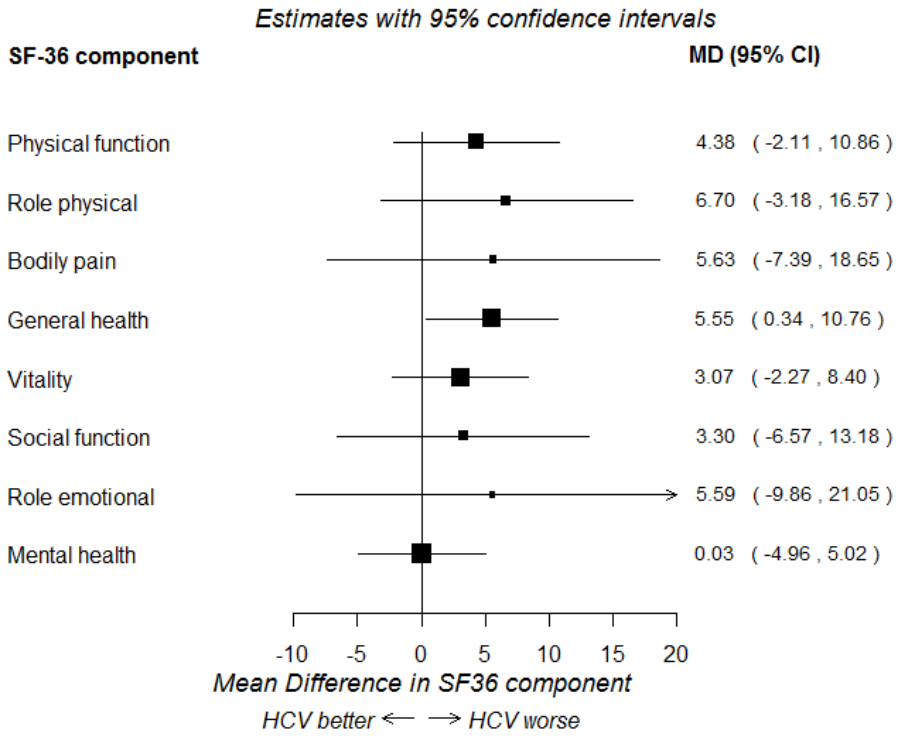


Figure 4.8: Mean difference in SF36 component scores in studies with HIV co-infection



4.6 Discussion

This analysis sought to examine whether chronic HCV infection is associated with poorer health-related quality of life. Taken together the findings of the 22 studies in the quality of life general population synthesis suggest that, compared to general or healthy populations, those with HCV are likely to perceive their physical and mental health as worse. Findings suggest that the impairment is both statistically and clinically significant. Indications from the meta-analyses and from individual studies are that physical health is affected to a greater degree than mental health.

Similarly, the findings from the seven studies in the synthesis comparing people with co-infection with HIV and HCV with people with HIV only suggest that people with co-infection are likely to have a lower quality of life, with physical health again being affected to a greater extent than mental health.

For the synthesis comparing people with HCV to the general population, both the large number of studies and the consistency in the direction of findings across all aspects of quality of life are indicators of the validity of the findings; however, it must be recognised that the strength of conclusions that can be drawn is severely undermined by both the low methodological quality of the studies and the fit between these studies and the population to which our review questions apply. In general, the set of studies located to address these research questions was weakened by questionable comparison groups and limited control or adjustment for

confounding factors. As studies typically matched on age and gender only, and there was little adjustment for other factors (notably PWID), the impairments to quality of life among people with HCV may be accounted for, at least in part, by other factors such as their socio-economic status or use of injection drugs. However, the consistency of findings across different HCV populations and comparison groups indicate that some potential confounders do not appear to impact on the findings. For example, among the 22 studies in the general population synthesis, all of which showed findings indicating impaired quality of life among HCV participants, ten included participants who were treatment naive, a further five indicated that HCV participants were not currently undergoing treatment, and in four studies participants had recently undergone or were currently in therapy. Similarly, country of origin did not appear to impact on the findings.

However, in relation to the general population synthesis, despite the large number of studies and the reaching of 100% consistency with regard to the direction of findings, since just two of the included studies were judged to be of moderate risk of bias and the remainder were all judged as being at high risk, the findings in relation to question a) can only be considered 'promising' (see Section 9.7 for the algorithm for grading evidence).

The findings in relation to question b) must also be considered only as promising. Despite identifying some studies which had a good fit with the scope of this review (i.e. they examined quality of life among HCV patients who had acquired the infection iatrogenically), the number of such studies was small (n=5), their samples were small and very specific (two studies included females only), only two were judged as being of moderate risk of bias (as opposed to high risk of bias) and just two were amenable to meta-analysis.

The findings from the HIV Quality of Life synthesis must be considered as tentative. Their strength is boosted by the consistency of the findings across the set as a whole; however, the findings are based on a small set of studies (n=7) and all but one study were rated as having a high risk of bias. It is also important to note that, since most studies either contained a majority of people likely to have been infected by injection drug use and/or sexual contact, or did not report risk factors for infection, the generalisability of the findings to people who have been infected iatrogenically is limited. The lack of exploration of levels of cirrhosis in the populations under study is also of concern.

Previous systematic reviews which have explored the association between HCV and quality of life (Groessl et al. 2007, Spiegel et al. 2005) also found evidence to suggest that clinically significant decrements in quality of life exist for patients with HCV, with some evidence that this is also the case for people co-infected with HIV. Whilst the current review provides an up-to-date assessment, it also provides new knowledge, as it goes further to mitigate the problems of poorly matched samples in many studies on HCV and quality of life and, unlike previous reviews, focuses specifically on chronic HCV by excluding studies which focused on patients with cirrhosis. The thorough examination and meta-analysis of evidence regarding

patients who acquired HCV iatrogenically and those co-infected with HIV also address previous gaps in knowledge.

5. Results: depression, anxiety and hepatitis C infection

5.1 Summary of findings

- A total of 22 studies met our inclusion criteria and were retrieved in time to be included in the synthesis.
- Studies were generally of poor methodological quality, which reduces the strength of the findings.
- Meta-analysis of 12 studies identified the severity of depression in people with HCV to be significantly greater than among those without HCV (MD 0.98, 95% CI 0.43-1.53).
- Meta-analysis of nine studies identified the severity of clinical anxiety among people with HCV to be significantly greater than among those without HCV (MD 0.47, 95% CI 0.09-0.86).
- Meta-analysis of seven studies found that participants with HCV were approximately three times as likely to be depressed compared to those without HCV (OR 2.77, 95% CI 1.62-4.74).
- Meta-analysis of three studies found no statistically significant evidence of an increase in the prevalence of anxiety among people with HCV.
- There was no evidence that depression or anxiety is more severe in people with HCV who are co-infected with HIV, compared to those infected with HIV alone (this finding is not the same as 'evidence of no relationship' between HCV and depression or anxiety in this group).
- Evidence regarding depression and anxiety among people who had acquired HCV iatrogenically was severely limited.

In this chapter, we examine the association between HCV infection and depression and anxiety, conditions identified by all four HCV advocacy groups as significant extrahepatic conditions experienced by people living with HCV. This chapter addresses the following:

Overarching question:

Are depression and anxiety associated with chronic HCV infection?

Specifically, we answered the following sub-questions relating to various comparisons between different groups with HCV:

1. Do people with HCV experience greater levels of depression and anxiety than people without HCV?
2. Do people who acquired HCV iatrogenically experience greater levels of depression and anxiety than those who acquired HCV through other routes?
3. Do people co-infected with HCV and HIV experience greater levels of depression and anxiety than those infected with HIV alone?

A total of 22 studies met our inclusion criteria and were retrieved in time to be included in the synthesis. These 22 studies were organised according to the types of comparison undertaken.

Of the 22 included studies, 19 examined depression or anxiety in groups infected with HCV alone and compared to groups without HCV; four studies assessed depression or anxiety in HCV-HIV co-infected groups compared to those infected with HIV only. One of the studies contained both comparisons. Separate analyses were undertaken for the nineteen studies of HCV-infected groups and the four studies of HCV-HIV co-infected groups.

5.2 Depression or anxiety in people with HCV compared to people without HCV

5.2.1 Description of included studies

Quality assessment

Study quality was limited overall. Of the 19 studies that compared people with HCV to people without HCV, only three described an appropriate comparison group, i.e., with comparable socio-demographic characteristics such as age, gender and rates of substance use (Carta et al. 2007, Heeren et al. 2013, Lowry et al. 2010). In several studies, significantly higher rates of drug and/or alcohol use were reported in HCV patients compared with controls. Only four studies made appropriate attempts to account for potential confounding (Carta et al. 2007, Heeren et al. 2013, Lowry et al. 2010, Lee et al. 2013), and of those, only one study used appropriate statistical methods (multivariate regression) to control for relevant confounders (Lee et al. 2013). Therefore, most studies were at high risk of confounding bias.

Only four studies (Carta et al. 2007, El-Serag et al. 2002, Lowry et al. 2010, Lee et al. 2013) reported sufficient information to suggest that their sample was likely to be representative of their population of interest (external validity). On the other hand, 16 out of 18 studies provided enough information to indicate that they had used appropriate methods to diagnose HCV, and all studies but one (Basseri et al. 2010) used a validated tool to measure depression and/or anxiety.

It is more challenging to determine whether the studies are representative of the population of interest in our review. The route of HCV acquisition was either unclear or primarily associated with drug use rather than iatrogenic infection in nearly all studies. However, six studies included differing proportions of patients with iatrogenically-acquired HCV (Ashrafi et al. 2012, Cordoba et al. 2003, Erim et al. 2010, Goulding et al. 2001, Heeren et al. 2013, Lowry et al. 2010). These ranged from 19 to 68 percent of iatrogenically infected participants, with one study only reporting PWID rates (Thein et al. 2007). Two studies examined samples who had all contracted HCV iatrogenically: one studied women who had contracted HCV during pregnancy from administration of anti-D immunoglobulin (Heeren et al. 2013); the other did not specify why patients had received blood products (Lowry et al. 2010). Further, all individuals included in studies of iatrogenically acquired HCV were either exclusively or largely female; thus findings may not be generalisable to male populations. Further, these studies were conducted in Ireland and Germany, which may limit the

applicability of their findings to the UK health care system. Although these two studies were considered to be of greater relevance to our population of interest, the extent to which their findings are directly generalisable to all types of iatrogenically acquired HCV patients in the UK should be subject to caution. Table A3.3 in Appendix 3 summarises quality judgements by study.

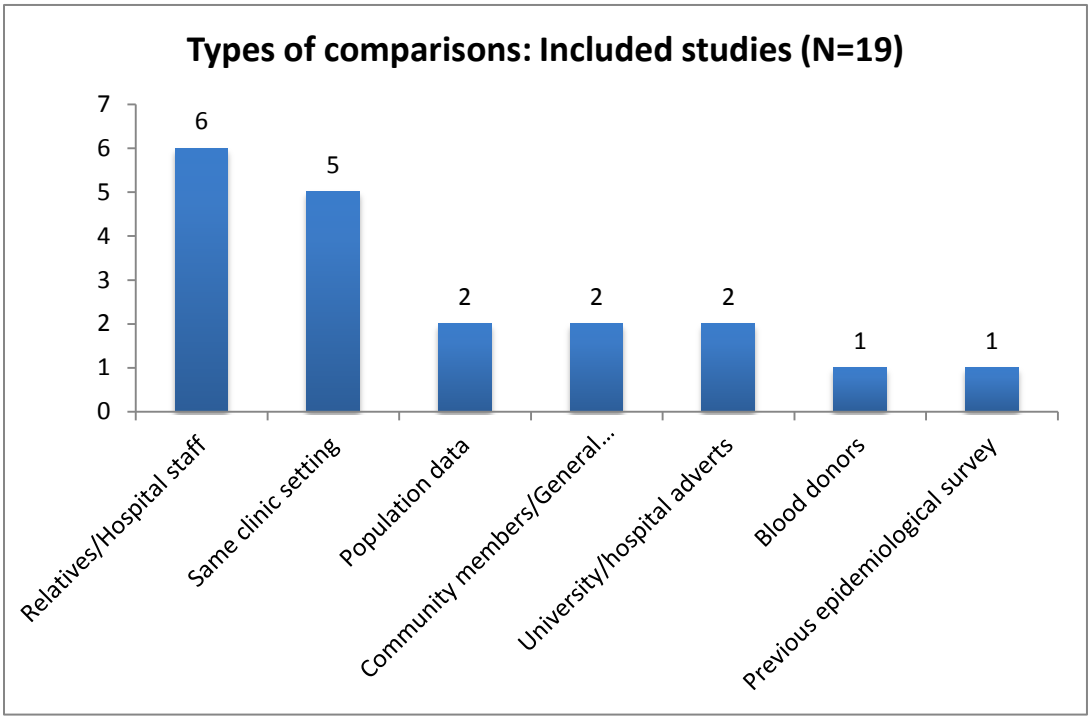
Country of origin, study setting, comparison groups

The studies were undertaken across many countries. Five of the included studies were undertaken in the USA, followed by two studies in each of the following countries: Germany, Greece, Iran, Ireland and Pakistan. One study was undertaken in each of Australia, Italy, Poland and Spain. No UK-based studies met our inclusion criteria.

Studies were largely undertaken in similar settings. Hospital-based specialist clinics treating patients with HCV were the settings for 16 of the 19 included studies; one study sampled from a support group for HCV patients (Heeren et al. 2013). The remaining two studies were broader in nature and drew their samples of comparisons and controls from a national veterans hospital system administrative database (El-Serag et al. 2002) and from a national survey of health (Lee et al. 2013).

A wide range of comparison groups was noted across the studies, as illustrated in Figure 5.1.

Figure 5.1: Types of comparison groups: Included studies (N=19)



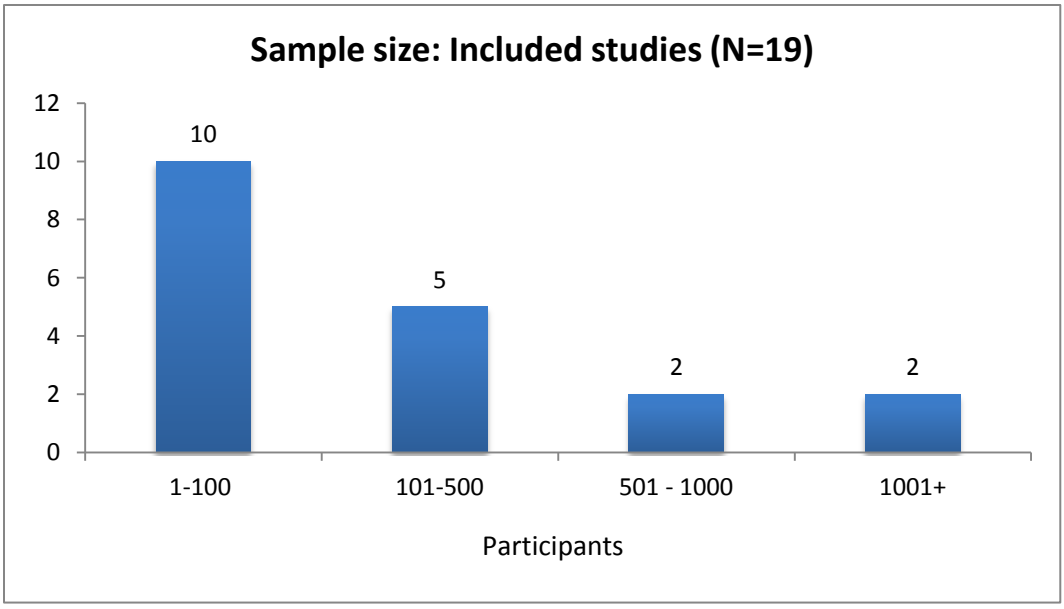
Only five of the included studies utilised an HCV-negative comparison group from the same setting (Danoff et al. 2006, El-Serag et al. 2002, Koskinas et al. 2002, Lee et al. 2013, Sun et al. 2013). Six studies compared HCV patients with their accompanying relatives and/or hospital staff (Cordoba et al. 2003, Gill et al. 2005, Goulding et al. 2001, Heeren et al. 2013, Karaivazoglou et al. 2007, Qureshi et al. 2012). Two studies each compared HCV patients with either: population data (Basseri et al. 2010, Erim et

al. 2010); participants from 'community' or 'general population' not further specified (Ashrafi et al. 2012; Malyszczak et al. 2010); or participants located through wider hospital or university advertisements (Lowry et al. 2010, Thein et al. 2007). Blood donors were recruited as comparison groups in one study (Alavian et al. 2007) and participants from a 'previous epidemiological survey' in one other study (Carta et al. 2007).

Study design, sample size

All studies included in the analysis were of cross-sectional design. No studies of longitudinal design were located (i.e. employing measurements of depression or anxiety at more than one time point). Samples ranged in size from 29 to 65,608 participants. Figure 5.2 illustrates the distribution of samples sizes across studies.

Figure 5.2: Distribution of sample size across studies (N=19)



In general, most studies were undertaken with small samples. Ten studies included samples of less than 100 (Alavian et al. 2007, Cordoba et al. 2003, Goulding et al. 2001, Heeren et al. 2013, Karaivazoglou et al. 2007, Koskinas et al. 2002, Lowry et al. 2010, Malyszczak et al. 2010, Sun et al. 2013, Thein et al. 2007). Another five studies had samples of between 101 and 500 participants (Ashrafi et al. 2012, Danoff et al. 2006, Erim et al. 2010, Gill et al. 2005, Qureshi et al. 2012). Two studies (Basseri et al. 2010, Carta et al. 2007) had between 501 and 1,000 participants. The former study examined measures of depression and anxiety in 800 American HCV patients compared to an unknown number of population controls. The latter study examined HCV and psychiatric illness in an Italian hospital-based sample. Two studies had over 1,000 participants: El-Serag et al. (2002) used hospitalisation records from an American veterans' hospital administration system; Lee et al. (2013) examined data from the US National Health and Nutrition Examination Survey (NHANES).

Participant demographics

The mean age of samples across the studies ranged from 39 to 56 years, and most often, the majority of participants were men. Men were studied exclusively in two reports (Danoff et al. 2006; Sun et al. 2013). The distribution of men in 15 studies ranged from 21% to 99%. Women were studied exclusively in two studies of exclusively iatrogenically infected participants (Heeren et al. 2013, Lowry et al. 2010). Effect sizes did not appear to differ in studies with predominantly male or female samples.

Route of HCV acquisition

Route of HCV acquisition was reported in one-third of the included studies. Only two of the included reports studied samples that were composed entirely of iatrogenically infected women (Heeren et al. 2013, Lowry et al. 2010). Four studies described a mixed route of HCV acquisition in samples and comparisons (Ashrafi et al. 2012, Cordoba et al. 2003, Erim et al. 2010, Goulding et al. 2001). None of these studies adjusted for differences in route of HCV acquisition in analysis or reported findings for separate groups by route of acquisition. The remaining thirteen studies did not report route of HCV acquisition.

Liver disease severity

The studies were divided in terms of controlling for liver disease: almost half (n=8) of the studies excluded patients with cirrhosis (Ashrafi et al. 2012, Danoff et al. 2006, Erim et al. 2010, Heeren et al. 2013, Karaivazoglou et al. 2007, Qureshi et al. 2012, Sun et al. 2013, Thein et al. 2007). Only Lowry et al. (2010) reported that their entire sample had minimal liver fibrosis. The remaining nine studies did not report liver disease severity.

Alcohol use

Just over half of the studies (n=10) excluded patients with a higher than average alcohol intake, although the threshold for 'high intake' varied across studies (Carta et al. 2007, Cordoba et al. 2003, Danoff et al. 2006, Goulding et al. 2001, Karaivazoglou et al. 2007, Koskinas et al. 2002, Lowry et al. 2010, Qureshi et al. 2012, Sun et al. 2013, Thein et al. 2007). Of the remaining studies, only three reported varying rates of alcohol use between groups: El-Serag (2002) noted a prevalence of alcohol use disorders in 78% of the HCV patients versus 46% in comparison subjects; Heeren et al. (2013) reported that 45% of the sample had light to moderate alcohol intake, compared to 74% in the comparison group; Lee et al. (2013) noted alcohol use in 78% of the HCV participants, compared to 0% in the control group. Only El-Serag (2002) reported analyses that adjusted for substance use. Six studies did not report either alcohol use or exclusions for alcohol use (Alavian et al. 2007, Ashrafi et al. 2012, Basseri et al. 2010, Erim et al. 2010, Gill et al. 2005, Malyszczak et al. 2010).

People who inject drugs

Inclusion of PWID in HCV samples has the potential to influence the identification of any relationship between depression and HCV status. However, only about one-third of the included studies appeared to control for this important confounding factor. A total

of six studies excluded PWID from their samples (Carta et al. 2007, Danoff et al. 2006, Heeren et al. 2013, Karaivazoglou et al. 2007, Malyszczak et al. 2010, Sun et al. 2013). Seven studies reported on rates of PWID in samples (Ashrafi et al. 2012, Basseri et al. 2010, Cordoba et al. 2003, El-Serag et al. 2002, Erim et al. 2010, Lee et al. 2013, Thein et al. 2007). These ranged from 2% (Cordoba et al. 2003) to 84% (Thein et al. 2007) and, like those studies that excluded injection drug users, could have classified PWID in a number of ways: examples included 'drug use', 'lifetime', 'history of' and 'current' injection drug use. One study excluded people with current injection drug use from their sample but measured history of injection drug use (Goulding et al. 2001). Only one study adjusted for injection drug use in analysis (Lee et al. 2013). The remaining five studies did not report whether they measured any rates of PWID.

Treatment for HCV

Two-thirds of the studies were designed to account for the potential influence of interferon (IFN) treatment: twelve of the studies excluded patients from the sample who either had a history of or were currently undergoing IFN therapy (Carta et al. 2007, Cordoba et al. 2003, Danoff et al. 2006, Erim et al. 2010, Goulding et al. 2001, Heeren et al. 2013, Karaivazoglou et al. 2007, Koskinas et al. 2002, Lowry et al. 2010, Malyszczak et al. 2010, Qureshi et al. 2012, Sun et al. 2013). Six studies did not specify the previous or current treatment status of patients in the sample (Alavian et al. 2007, Ashrafi et al. 2012, Basseri et al. 2010, El-Serag et al. 2002, Gill et al. 2005, Lee et al. 2013). One study reported past history of IFN treatment (Erim et al. 2010). No studies reported separate analyses for treated and untreated groups.

Previous psychiatric / neurocognitive diagnosis

Similarly, just over half (n=10) of the studies controlled for the confounding influence of previous or existing psychiatric or neurocognitive disorders by excluding patients with these characteristics from the sample (Ashrafi et al. 2012, Cordoba et al. 2003, Heeren et al. 2013, Karaivazoglou et al. 2007, Koskinas et al. 2002, Lowry et al. 2010, Malyszczak et al. 2010, Qureshi et al. 2012, Sun et al. 2013, Thein et al. 2007). Erim et al. (2010) reported that 29.4% of the HCV patients had had previous psychiatric treatment but neither reported the rate in the comparison group nor adjusted for differences. The remaining eight studies did not report on psychiatric or neurocognitive disorders.

HCV measures

Two-thirds of the studies indicated that HCV infection was chronic in nature: a total of twelve studies confirmed current HCV infection by RNA polymerase chain reaction testing. Only one of these differentiated between HCV patients who had cleared the virus and those who were viraemic (Lowry et al. 2010). Alavian et al. (2007) considered patients HCV-infected if they had two positive anti-HCV antibody tests within six months of each other. The remaining six studies did not report how HCV status was measured (Basseri et al. 2010, Carta et al. 2007, Erim et al. 2010, Heeren et al. 2013, Koskinas et al. 2002, Malyszczak et al. 2010).

Depression/anxiety measures

A wide range of measures was used to detect anxiety or depression in this set of studies, as shown in Table 5.1.

Table 5.1: Depression and anxiety measures used (n=19)

Study	HADS	BDI	DSM-IV	Other
Alavian et al. (2007)	✓			
Ashrafi et al. (2012)	✓			
Basseri et al. (2010)				clinical diagnosis
Carta et al. (2007)			✓	
Cordoba et al. (2003)		✓		STAI
Danoff et al. (2006)		✓		
El-Serag et al. (2002)			✓	
Erim et al. (2010)	✓	✓		
Gill et al. (2005)				BAI
Goulding et al. (2001)	✓			
Heeren et al. (2013)	✓	✓		
Karaivazoglou et al. (2007)		✓		
Koskinas et al. (2002)				SDS
Lee et al. (2013)				PHQ-9
Lowry et al. (2010)	✓			
Malyszczak et al. (2010)			✓	
Qureshi et al. (2012)	✓			
Sun et al. (2013)		✓		
Thein et al. (2007)				DASS

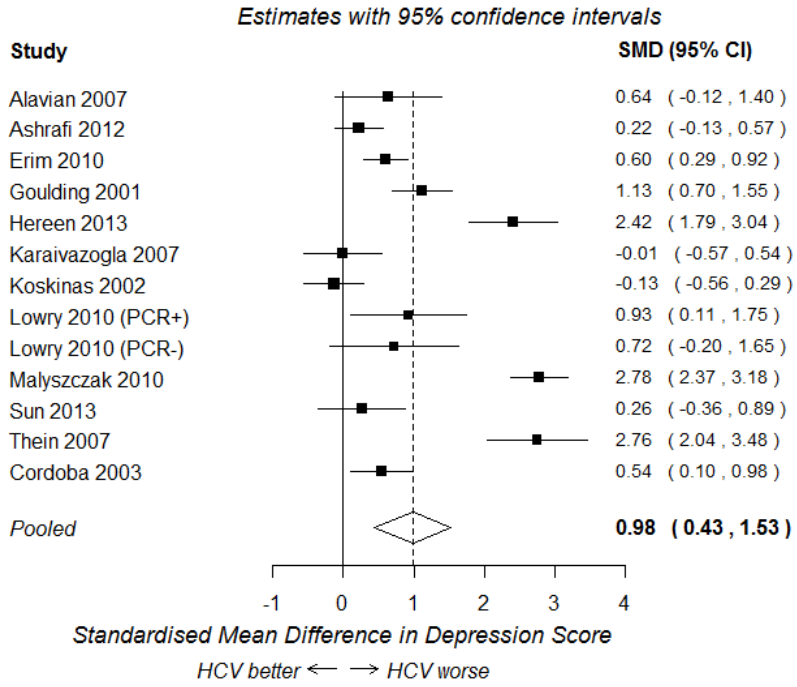
Three studies used more than one measure (Cordoba et al. 2003, Erim et al. 2010, Heeren et al. 2013). The Hospital Anxiety and Depression Scale (HADS) was used most often (n=7), followed by the Beck Depression Inventory (BDI) (n=6) and DSM-IV diagnosis (n=3). One study each used the Beck Anxiety Inventory (BAI), Stress and Depression Scales (SDS), the Patient Health Questionnaire version 9 (PHQ-9) and the

Depression, Anxiety Stress Scales (DASS). Some studies used more than one measure. The interpretation of depression and anxiety scores varied somewhat between studies. For example, Alavian et al. (2007) interpreted scores of greater than 11 as denoting depression, while Ashrafi et al. (2012) determined depression from scores which were in the 75th centile. Appendix 5 provides a detailed explanation of interpretations for each measure.

5.2.2 Findings: depression

Twelve studies reported on severity of depression among people with HCV compared to those without HCV (mean depression scores according to presence or absence of HCV). One study provided results for both PCR positive and PCR negative individuals (Lowry et al. 2010). The forest plot of the standardised mean difference for these studies is shown in Figure 5.3.

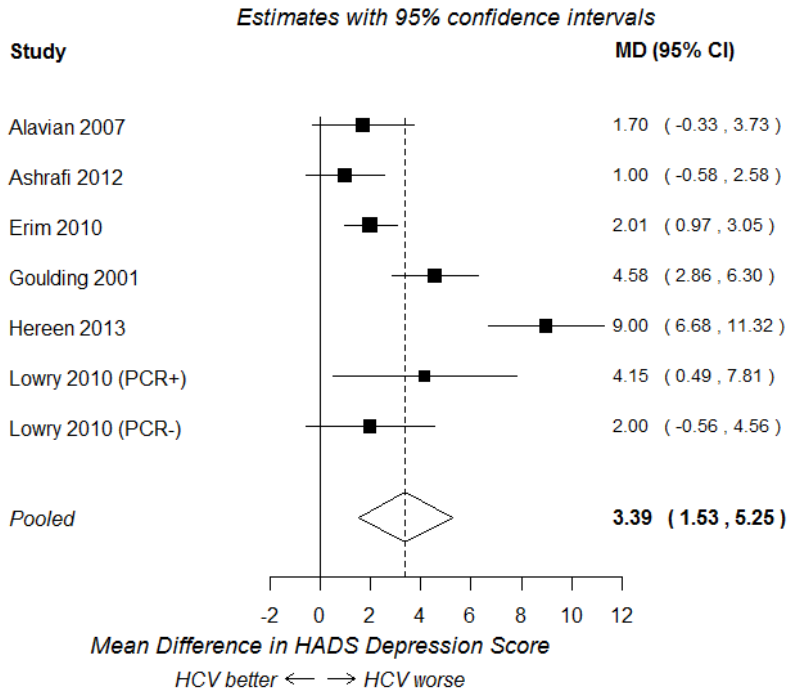
Figure 5.3: Meta-analysis of standardised mean difference in depression score



Depression scores are worse in people with HCV by about one standard deviation. For the HADS scale, this translates into depression scores about four points higher with HCV, as the typical standard deviation in HADS score is around four points. It can be seen that there is very substantial heterogeneity across studies (I^2 = 94%). There was, however, no evidence that age, gender or injection drug use had any impact on the results. There was no evidence of publication bias.

Six studies presented results using the HADS scale. A meta-analysis of the mean differences in these studies is presented in Figure 5.4.

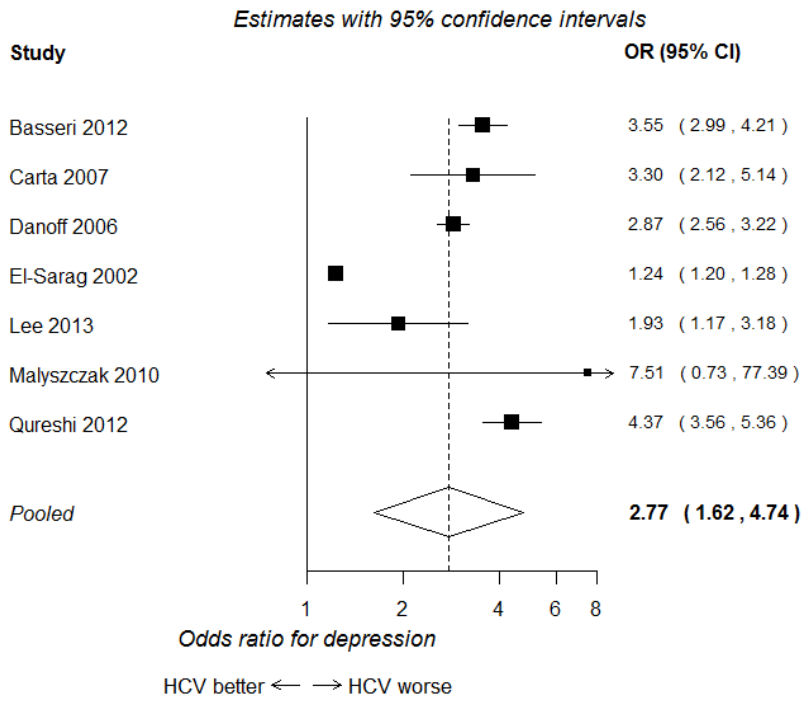
Figure 5.4: Meta-analysis of mean difference in HADS depression score



This shows that people with HCV have, on average, a depression score 3.4 points higher (indicating more severe depression) than people without HCV. This result is broadly consistent with the result from Figure 5.3. Heterogeneity was also high in this analysis (I^2 = 85%). This suggests that differences between measurement scales are unlikely to be a cause of the observed heterogeneity.

Seven studies reported prevalence of depression among people with HCV compared to those without HCV; of these, two (El Serag et al. 2002, Lee et al. 2013) presented adjusted odds ratios. The forest plot for these studies is shown in Figure 5.5.

Figure 5.5: Meta-analysis of prevalence of depression



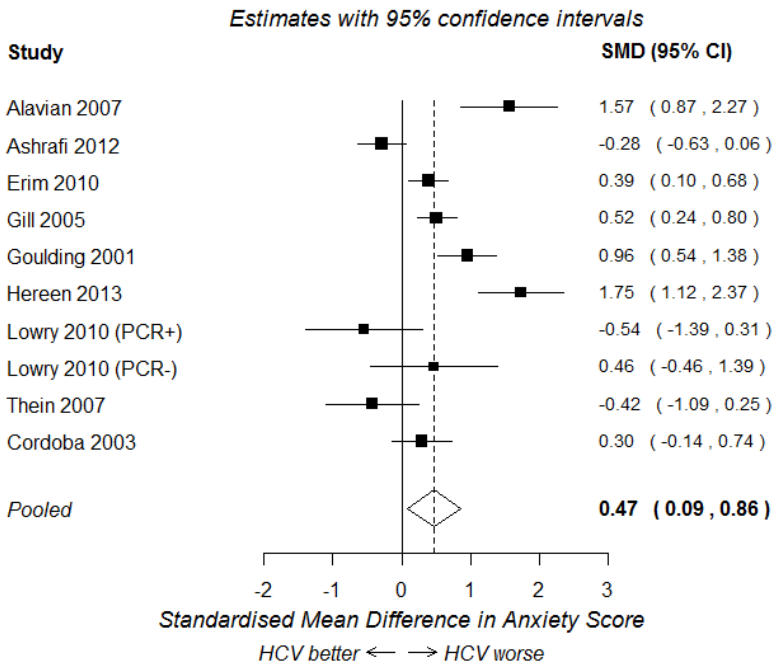
This suggests that depression is almost three times as prevalent among people with HCV. Heterogeneity is very high in this analysis (I^2 = 99%), calling into doubt the validity of pooling these studies. A fixed-effect meta-analysis gives a very different result (OR 1.40, 95% CI 1.36-1.45), and is dominated by the El-Serag et al. (2002) study. This suggests that depression prevalence may be confounded with factors other than HCV in this analysis, making unadjusted results unreliable. There may also be problems with selective reporting of depression results, as Egger's test for funnel plot asymmetry gave an almost statistically significant result (p = 0.056).

From a meta-regression, there was some evidence that prevalence of depression among HCV patients increased with average age (OR 1.46 per year, p = 0.026), although this was based on limited data. There was no evidence that gender or drug use affected the results.

5.2.3 Findings: anxiety

Nine studies reported on the severity of anxiety (mean anxiety scores) according to presence or absence of HCV. The forest plot of the standardised mean difference for these studies is shown in Figure 5.6.

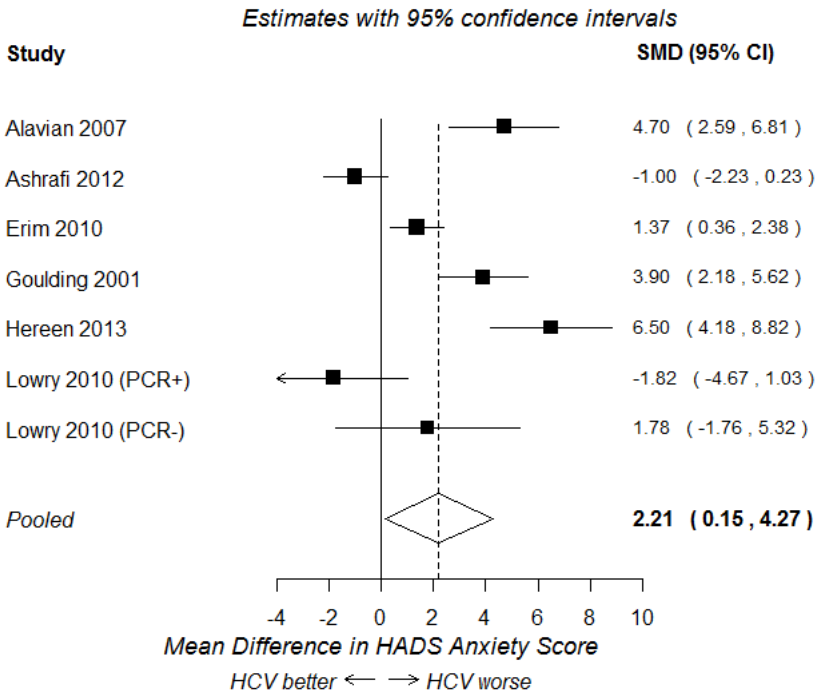
Figure 5.6: Meta-analysis of standardised mean difference in anxiety score



Anxiety scores are worse in people with HCV by about half of one standard deviation. For the HADS scale, this translates into anxiety scores about two points higher with HCV. It can be seen that there is very substantial heterogeneity across studies (I^2 = 85%), and some studies found that anxiety was no worse, or better in people with HCV. There was, however, no evidence that age, gender or injection drug use had any impact on the results.

Six studies presented results using the HADS scale. A meta-analysis of the mean differences in these studies is presented in Figure 5.7.

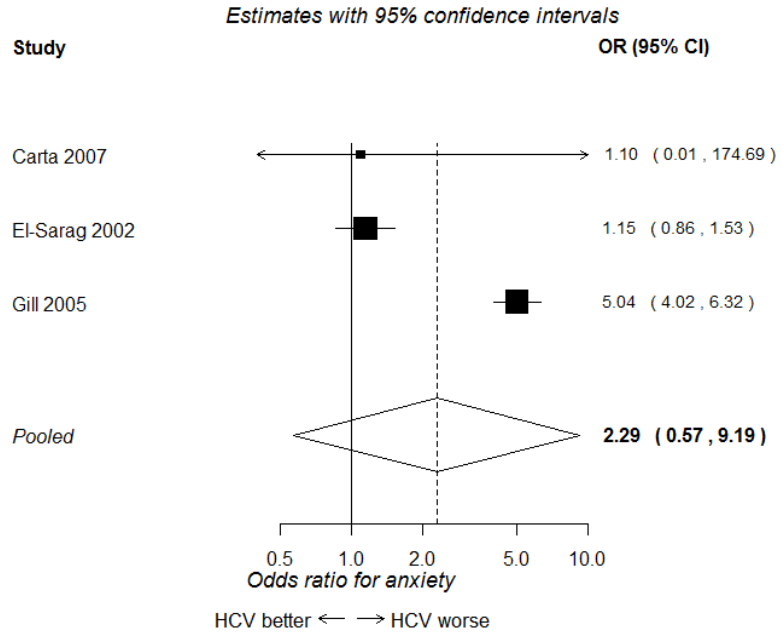
Figure 5.7: Meta-analysis of mean differences of anxiety



This shows that people with HCV have, on average, an anxiety score 2.2 points higher (indicating more severe anxiety) than people without HCV. This result is broadly consistent with the result from Figure 5.6. Heterogeneity was also high in this analysis (I^2 = 89%).

Three studies reported prevalence of anxiety. The forest plot for these studies is shown in Figure 5.8. There is no statistically significant evidence of an increase in the rate anxiety among people with HCV.

Figure 5.8: Meta-analysis of prevalence of anxiety



5.2.4 Findings: studies with iatrogenically infected samples

Only two studies examined participants who were all iatrogenically infected, a number too small to undertake meta-analysis. Narrative synthesis of these two studies indicates inconsistent results. Heeren et al. (2013) noted a statistically significant difference in HADS scores of depressed HCV patients, compared to healthy controls (MD 9.0 95% CI 6.68-11.32). However, Lowry et al. (2010) found a statistically significant difference in the HADS scores for PCR-positive subgroups only (MD 4.15, 95% CI 0.49-7.81) and a non-statistically significant difference for PCR-negative subgroups (MD 2.00, 95% CI -0.56-4.56). This suggests a trend toward a relationship between depression and HCV in those who have acquired it iatrogenically, but the strength of these findings must be tempered by consideration of the non-representative comparison groups and little adjustment for imbalances in key characteristics between groups.

5.3 Depression or anxiety in HCV-HIV co-infected groups

5.3.1 Description of included studies

A total of four studies examined prevalence of depression or anxiety in groups co-infected with HCV and HIV (Clifford et al. 2005, Thein et al. 2007, Von Giesen et al. 2004, Yoon et al. 2011).

Quality assessment

All four included studies were assessed for methodological rigour. Two of these described an appropriate comparison group or made appropriate attempts to account for potential confounding (Von Giesen et al. 2004, Yoon et al. 2011). Three reported sufficient information to suggest appropriate external validity (Clifford et al. 2005,

Von Giesen et al. 2004, Yoon et al. 2011). All used reliable measures of HCV status and relevant outcomes. Only one study from Germany reported separate data on a small subgroup of patients who acquired HCV by blood products (Von Giesen et al. 2004).

Table A3.4 in Appendix 3 summarises the quality judgements by study.

Country of origin, study setting, comparison groups

The studies were undertaken in America, Australia and Germany. Clifford et al. (2005) analysed patients enrolled in a drug trial in an undescribed setting and Thein et al. (2007) enrolled patients from a drug trial at a hepatitis clinic; Von Giesen et al. (2004) and Yoon et al. (2011) enrolled patients from a specialist treatment clinic. Comparison groups were assembled from the same setting in three of the studies (Clifford et al. 2005, Von Giesen et al. 2004; Yoon et al. 2011), while one study described the comparison group as university students and staff members (Thein et al. 2007).

Study design, sample size

All four studies were cross-sectional analyses of data collected at one point in time. One study had over 700 participants (Yoon et al. 2011); two studies had samples between 100 and 500 participants (Clifford et al. 2005, Von Giesen et al. 2004). Thein et al. (2007) had a sample size of less than 100 participants.

Participant demographics

Participants in the study by Clifford et al. (2005) were predominantly male (77%) and middle-aged (40.27 years ± 7.75). Thein et al. (2007) studied a completely male sample with a mean age of 35.5 years (±7.0). Von Giesen et al. (2004) studied a sample that was predominantly male (65.1%) with a mean age of 37.4 ±7.8 years. Yoon et al. (2011) studied participants of predominantly male gender (87%) with a median age of 45 years. Clifford et al. (2005) reported similar total years of education between HCV and comparison patients ($p<0.001$), although groups differed on ethnicity in that the HCV group had a higher proportion of Hispanics and the HCV-negative group had more Caucasians. Thein et al. (2007) reported that 74% and 26% of the sample completed secondary and tertiary education respectively.

Only one study matched participants on age and gender (Thein et al. 2007). Von Giesen et al. (2004) reported groups as equivalent on measures of age and gender. Clifford et al. (2005) noted imbalances between groups on education but did not correct for this in analysing the associations between depression and anxiety and HCV. Yoon et al. (2011) noted imbalances between groups in terms of age, gender and ethnicity and corrected for these in the analysis.

Route of acquisition

None of the four studies examined samples of patients with completely iatrogenically acquired HCV. The route of HCV acquisition was described in only one study (Von Giesen et al. (2004). Here groups were not significantly different in terms of method of acquisition.

Clifford et al. (2005) reported PWID rates of 47%, and differences between groups on this variable were adjusted for in analysis. Rates of PWID were 62.8% in the study by Von Giesen et al. (2004); patients with and without a history of drug use were analysed separately to allow for the potential influence of drug use.

Liver disease severity

Clifford et al. (2005) and Yoon et al. (2011) did not describe exclusions for or rates of liver disease severity or cirrhosis. Von Giesen et al. (2004) and Thein et al. (2007) excluded patients with cirrhosis but did not report on liver disease severity in included participants.

Alcohol use

Thein et al. (2007) excluded participants with a history of alcohol intake more than 100 g per week. Yoon et al. (2011) reported at-risk alcohol use of 16% and 17% for HCV-HIV co-infected and HIV-positive groups respectively. Alcohol use was not reported in the other two studies.

People who inject drugs

All four of the studies examining co-infected patients described the rates of PWID. Clifford et al. (2005) reported a rate of 47% PWID, while Thein et al. (2007) differentiated between PWID within the past twelve months (5%) and PWID 12 months ago or longer (84%). Von Giesen et al. (2004) noted a PWID rate of 63%. Yoon et al. (2011) noted current illicit drug use in 42% of HCV- and HIV-positive participants and in 20% of HIV-positive comparison participants. Clifford et al. (2005), Von Giesen et al. (2004) and Yoon et al. (2011) adjusted for PWID in their analyses.

Treatment for HCV

Three studies accounted for the potential confounder of interferon treatment: Clifford et al. (2005) and Yoon et al. (2011) excluded those with previous interferon treatment, while Von Giesen et al. (2004) described sample and comparison groups equivalent on type of ART treatment (including untreated). Thein et al. (2007) did not describe the treatment status of participants.

Previous psychiatric/neurocognitive diagnosis

Von Giesen et al. (2004) and Thein et al. (2007) excluded patients with a history of central nervous system infection, hepatic encephalopathy or HIV-associated dementia. Neither Clifford et al. (2005) nor Yoon et al. (2011) described screening or measuring for a previous history of neurocognitive function or psychiatric disorders.

HCV measures

Measures of HCV were consistent across studies: all four reported HCV diagnosis by RNA testing, although Yoon et al. (2011) reported that HCV was measured by antibody-positive HCV or RNA or genotype measures.

Depression/anxiety measures

Each study utilised a different measure of depression or anxiety. Clifford et al. (2005) utilised the CES-D and SAI (State Anxiety Inventory) scales to measure depressive symptomatology and clinically significant anxiety respectively. Thein et al. (2007) used the Depression Anxiety Stress Scales (DASS). Von Giesen et al. (2004) used the Hamilton Depression rating scale (HDRS). Yoon et al. (2011) used the PHQ-9 rating scale, and adjusted in the regression analysis for the curvilinear relationship between standard scores and levels of depression using Item response theory.

5.3.2 Findings: depression and anxiety

Two studies examined the incidence of depression in HCV and HIV co-infected groups compared to HIV infected controls (Clifford et al. 2005, Yoon et al. 2011). Three studies compared severity of depression among people co-infected with HCV and HIV to controls with HIV only (Clifford et al. 2005, Thein et al. 2007, Von Giesen et al. 2004), and all three used different scales to measure depression. Two studies also reported severity of clinical anxiety as an outcome, also using different scales (Clifford et al. 2005, Thein et al. 2007). Figure 5.9 illustrates the meta-analysis of incidence of depression, Figure 5.10 shows the meta-analysis of standardised mean difference in depression scores and Figure 5.11 shows the meta-analysis of standardised mean difference in anxiety scores.

Figure 5.9: Meta-analysis of incidence of depression in people co-infected with HCV and HIV

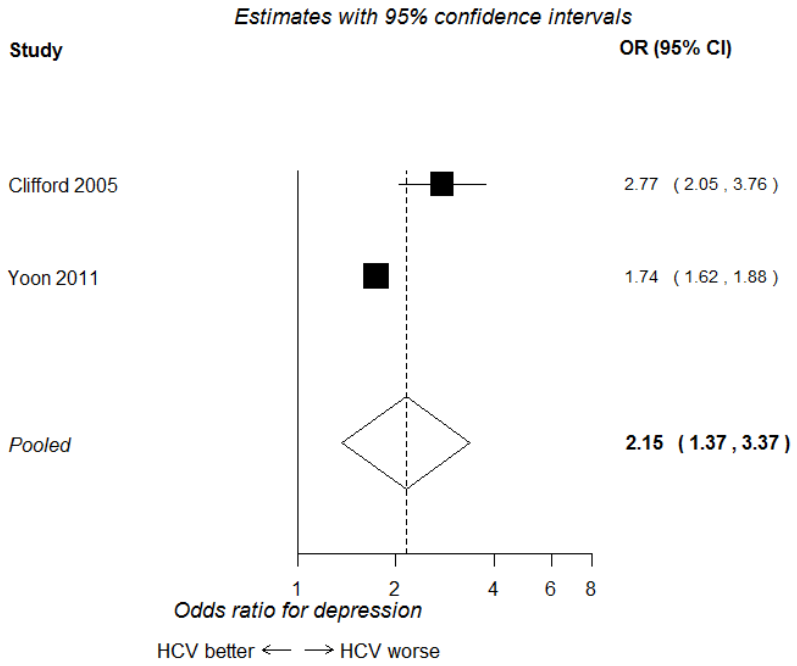


Figure 5.10: Meta-analysis of standardised mean difference in depression score in people co-infected with HIV

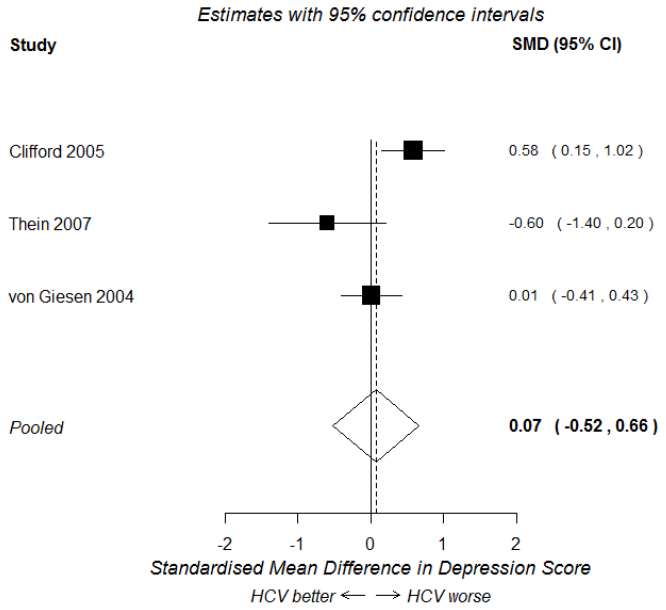
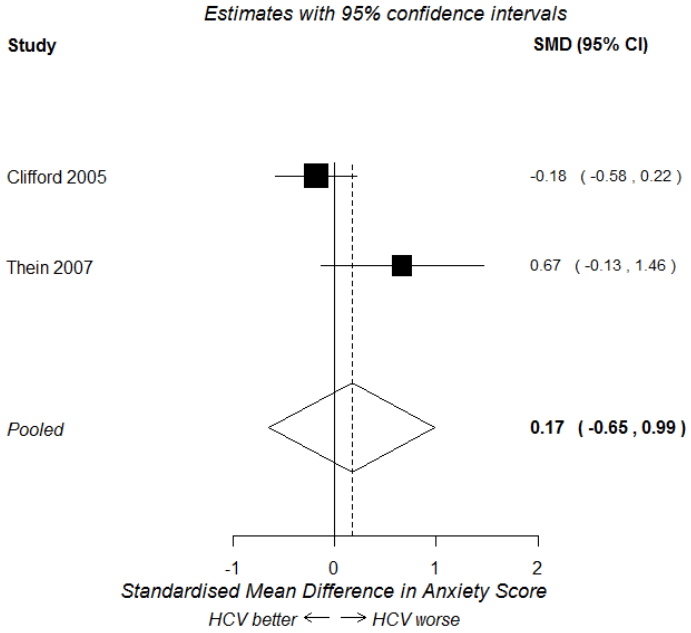


Figure 5.11: Meta-analysis of standardised mean difference in anxiety score in people co-infected with HIV



As illustrated by the forest plots, we found evidence from two studies indicating that the incidence of depression is more likely in people with HCV who are co-infected with HIV, compared to those infected with HIV only. However, there is no evidence that depression or anxiety is more severe in people with HCV who are co-infected with HIV, compared to those infected with HIV alone. (Note: this finding is not the same as 'evidence of no relationship' between HCV and severity of depression or anxiety).

5.3.3 Findings: studies with iatrogenically infected samples

None of the four included studies examining depression in HCV-HIV co-infected groups focused on exclusively iatrogenically infected samples. Only Von Giesen et al. (2004) described the route of HCV acquisition; in this study, only 16% were iatrogenically infected. Thus, we were not able to draw conclusions regarding depression and anxiety among people with HIV who had contracted HCV iatrogenically.

5.4 Discussion

This analysis sought to examine whether depression or anxiety are associated with chronic HCV infection and the strength of this relationship in people living with HCV.

Evidence from included studies indicates that depression and anxiety are more severe and depression is more common among people with HCV compared to people without HCV. No statistically significant evidence that anxiety is more common among people with HCV was found. A very small number of studies showed a higher likelihood of depression, but no evidence that depression or anxiety is more severe in people with HCV who are co-infected with HIV, compared to those infected with HIV alone. Evidence regarding the impact of the route of infection on outcomes was limited and inconsistent. While all of these findings are important, they must be tempered by both the high risk of bias within most of the studies and the fit between these studies and the populations to which our review questions apply.

In general, the set of studies located to address these research questions was complicated by questionable comparison groups and limited control or adjustment for confounding factors (i.e. matched on age and gender only, little adjustment for PWID). A large proportion of the studies in the meta-analyses of depression and anxiety scores in people with HCV versus people without HCV groups were judged to be at high risk of bias due to poor design or conduct. However, this dataset includes three studies that were at moderate risk of bias and, for both depression and anxiety, over 70% of the studies agreed on the direction of findings. This is sufficient for grading the evidence as 'promising' for the relationship between both depression and anxiety and HCV in HCV mono-infected patients (GRADE Working Group 2004, Sutcliffe et al. in press).

The biologic mechanisms underlying depression/anxiety in HCV patients are unclear. Some studies have examined the role of tryptophan and cortisol in HCV populations undergoing interferon treatment (Comai et al. 2011, Eccles et al. 2012, Gess et al. 2009). However, the nature of these studies makes it difficult to separate out the individual impacts of HCV and treatment on depression/anxiety. Other studies of HCV patients who were studied prior to interferon treatment controlled for the potentially confounding influence of treatment. These studies suggested evidence for a causal link with cytokine-mediated responses (Loftis et al. 2008, Wichers et al. 2006).

Depression and anxiety among people with HCV may be, at least in part, socially determined, for example through issues such as stigma, inability to disclose, difficulties in forming sexual relationships, and negative experiences with the medical system that may be experienced by people living with HCV (Groessl et al. 2007, Strauss and Teixeira 2006). Depression and anxiety may also be psychologically determined: knowledge of HCV status itself may influence depressive states (Rodger et al. 1999), although some evidence suggests that people who are HCV-positive, but have not yet been made aware of their diagnosis, still have higher rates of depression/anxiety (Strauss et al. 2013, Teixeira et al. 2006).

The included studies are only measuring association, not causation, so we cannot infer that HCV 'causes' depression, only that the two tend to be seen together. It is possible that people who are depressed tend to inject drugs, putting them at risk of HCV. Under ideal conditions, a sizeable dataset of longitudinal studies examining the causal relationship between depression or anxiety and HCV would have been available for assessment. However, we were able to locate no longitudinal studies. Furthermore, very few studies focused on people who have received HCV iatrogenically, and many had sizeable numbers of PWID in their samples, making generalisability of findings to iatrogenically infected populations difficult.

Importantly, despite consistent measurement of HCV by RNA polymerase chain reaction, these studies did not further differentiate between HCV patients who had naturally cleared the disease and those who were currently viraemic. We note that 'mono'-infected does not differentiate between those who spontaneously cleared the virus without treatment, those who cleared with treatment, and those who did not clear with treatment. The association with depression and/or anxiety in these groups may differ, but this cannot be established from this set of studies.

Finally, the location, assessment and synthesis of the research evidence on the relationship between depression, anxiety and HCV infection revealed a significant gap in literature focused specifically on iatrogenically infected populations, particularly for the UK. To inform current UK health policy relevant to this population, this stands as a pressing research need.

6. Results: pain and hepatitis C infection

6.1 Summary of findings

- Overall, the quality of evidence available to assess the relationship between HCV status and pain or painful conditions was limited, with only 5 of 26 studies making adjustments for potential confounders in their analyses.
- A meta-analysis of four studies comparing arthralgia prevalence between people with and without HCV infection suggested that being infected with HCV is associated with a 17% increase in the prevalence of arthralgia (RR 1.17, 95% CI 1.04-1.31, I2 = 8%). However, it is possible that the observed results may be due to confounding in the observational studies examined.
- One cross-sectional study, at moderate risk of bias, provided tentative evidence that there was no significant association between anti-HCV antibody/HCV RNA positivity and either probable or possible rheumatoid arthritis.
- A meta-analysis of five studies comparing fibromyalgia prevalence between people with and without HCV infection provided promising evidence to suggest that being infected with HCV is associated with an increase in the prevalence of fibromyalgia irrespective of the co-morbidities of those with HCV infection or the health status of the comparison group.
- One small study at moderate risk of bias examining 49 US veterans provided tentative evidence that there was no significant association between viral load and pain intensity.
- One study at moderate risk of bias provided tentative evidence to suggest that acquisition of HCV through blood transfusion was independently associated with the presence of fibromyalgia syndrome in 106 patients with chronic HCV infection.
- Four studies examining different extrahepatic pain outcomes (joint pain, musculoskeletal pain, presence of fibromyalgia and pain intensity) in patients with varying degrees of liver disease severity failed to demonstrate a relationship between severity of liver disease and extrahepatic pain or painful conditions.

This chapter addresses the following overarching review questions:

1. Which pain-related extrahepatic conditions are associated with chronic HCV infection?
2. Which groups of people with chronic HCV are affected by pain-related extrahepatic conditions?

Specifically, the following sub-questions relating to the association between HCV infection and pain or painful conditions have been addressed:

- Is there an association between HCV infection and arthralgia?
- Is there an association between HCV infection and arthritis?
- Is there an association between HCV infection and fibromyalgia?

- Is there an association between route of HCV infection and pain?
- Is there an association between liver disease severity and pain?

One systematic review examining a possible association between fibromyalgia syndrome (FS) and HCV infection was located (Chamizo-Carmona 2005). However, it did not specifically focus upon the relationship between HCV infection and FS, was published in Spanish, and is not considered further in this report.

A total of 29 studies met the eligibility criteria for inclusion in a synthesis relating to pain outcomes. However, two were not obtainable in the time available (Afifi et al. 2007, Al Sayed et al. 2001), and one further study (Zerrak et al. 2005) examined the same population of patients as another included study (Maillefert et al. 2002). To avoid double counting and overrepresentation of this population of patients, we have used only the findings of Maillefert et al. (2002) in this review, leaving a total of 26 studies included in the synthesis.

6.2 Description of studies

The methodological rigour, country of origin and metrics for the outcomes examined in the 26 included studies are presented in Table 6.1; further detail on each of the studies is presented in Tables A4.5 – A4.13 in Appendix 4.

Quality assessment

Of the 26 studies included in this synthesis, seven were judged to be at moderate risk of bias following appraisal with a standardised quality assessment tool. Nineteen studies were categorised as being at high risk of bias due to methodological flaws liable to invalidate the findings. No studies were found to be at low risk of bias. The appraisal of the methodology of the 26 studies is presented in more detail in Table A3.5 in Appendix 3.

Country of origin

We have examined all the international evidence available. Six studies were conducted in the US, five in Italy, four in Spain, three in France, two in Ireland, three in Turkey, one in Iran, one in Israel and one in the UK (See Table 6.1). The relatively high number of studies from Italy and Spain may reflect the comparatively high prevalence of HCV amongst the populations of these countries (Cornberg et al. 2011).

Pain states and/or painful conditions

Eleven studies examined the relationship between HCV status and the presence of arthritis, seven examined the relationship between HCV status and arthralgia (joint pain), and nine examined the relationship between HCV status and the presence of fibromyalgia syndrome (FS, otherwise known as fibromyalgia), as shown in Table 6.1. Three studies examined more than one of the above conditions (De Vita et al. 2002, Rivera et al. 1997, Yucel et al. 2005).

Three additional studies examined disparate pain outcomes including ‘musculoskeletal pain’ as assessed by questionnaire and pain diagrams scored by a rheumatologist (Barkhuizen et al. 1999), chronic widespread pain (CWP) as assessed via CWP

Manchester criteria (Isaacs et al. 2013) and pain intensity as measured by a numeric rating scale (Morasco et al. 2010).

Of the eleven studies examining the relationship between HCV status and the presence of arthritis, six diagnosed arthritis according to American College of Rheumatology criteria.

Of the nine studies examining the relationship between HCV status and the presence of fibromyalgia syndrome (FS), otherwise known as fibromyalgia, eight diagnosed FS according to American College of Rheumatology criteria.

The seven studies examining the relationship between HCV status and the presence of arthralgia used a variety of measures/diagnoses of arthralgia, as shown in Table 6.1.

Table 6.1: Association between HCV status and pain or painful conditions: methodological quality, country and outcome metrics (n = 26 studies).

Study	Risk of bias	Country	Arthralgia	Arthritis	Fibromyalgia (FS)	Pain
Baffoni et al. (1993)	HIGH	Italy		1987 ACR criteria		
Banks et al. (2007)	MODERATE	US	Questionnaire			
Barkhuizen et al. (1999)	HIGH	US				Musculoskeletal pain
Borque et al. (1991)	HIGH	Spain		1987 ACR criteria		
Buskila et al. (1997)	MODERATE	Israel			1990 ACR criteria	
Calore et al. (2012)	HIGH	US	Undergoing arthroplasty			
Congia et al. (1996)	HIGH	Italy		NR		
D'Amico et al. (1996)	HIGH	Italy		ARA criteria		
De Vita et al. (2002)	HIGH	Italy	'Clinical Evaluation'	'Clinical Evaluation'	'Clinical Evaluation'	
Gharagozloo et al. (2001)	HIGH	Iran		NR		
Goulding et al. (2001)	HIGH	Ireland			ACR criteria	
Guennoc et al. (2009)	HIGH	France		1987 ACR criteria		
Hsu et al. (2003)	MODERATE	US		1987 ACR criteria		

Study	Risk of bias	Country	Arthralgia	Arthritis	Fibromyalgia (FS)	Pain
Isaacs et al. (2013)	HIGH	UK				Manchester criteria
Kandemir et al. (2006)	HIGH	Turkey			Visual Analogue Scale	
Kozanoglu et al. (2003	HIGH	Turkey			1990 ACR criteria	
Maillefert et al. (2002)	HIGH	France		ACR criteria		
Mohammad et al. (2012)	MODERATE	Ireland			1990 ACR criteria	
Morasco et al. (2010)	MODERATE	US				Numeric Rating Scale
Narvaez et al. (2005)	HIGH	Spain			1990 ACR criteria	
Palazzi et al. (2008)	MODERATE	Italy			1990 ACR criteria	
Rieu et al. (2002)	HIGH	France	NR			
Rivera et al. (1997)	HIGH	Spain	Physical Examination		1990 ACR criteria	
Rivera et al. (1999)	HIGH	Spain		1987 ACR criteria		
Tsui et al. (2012)	MODERATE	US	HIV Symptom Index			
Yucel et al. (2005)	HIGH	Turkey	Questionnaire/MR	Questionnaire/MR		

NR = Not reported; ACR = American College of Rheumatology; ARA = American Rheumatism Association; MR=Medical Records

Measures of HCV infection

Twenty-five included studies reported that the presence of HCV infection was determined by testing for the presence of anti-HCV antibodies. Sixteen of 26 studies also tested for the presence of HCV RNA. As Barkhuizen et al. (1999) note, ideally patients with evidence of past infection (i.e. presence of anti-HCV antibodies) should also have a test for the presence of HCV RNA to confirm active infection.

Studies in which the population under investigation was described as having 'chronic' HCV infection, or that carried out additional tests to assess whether HCV RNA was present, are shown in Table 6.2.

Table 6.2: Association between HCV status and pain or painful conditions: studies describing HCV infection as 'chronic', or determining the presence of active infection by testing for HCV RNA (n = 26 studies)

Study	HCV infection described as 'chronic'	Test for HCV RNA
Baffoni et al. (1993)		
Banks et al. (2007)	✓	
Barkhuizen et al. (1999)	✓	
Borque et al. (1991)		
Buskila et al. (1997)	✓	✓
Calore et al. (2012)		✓
Congia et al. (1996)	✓	
D'Amico et al. (1996)	✓	
De Vita et al. (2002)	✓	✓
Gharagozloo et al. (2001)		
Goulding et al. (2001)	✓	✓
Guennoc et al. (2009)		
Hsu et al. (2003)		✓
Isaacs et al. (2013)		
Kandemir et al. (2006)	✓	✓
Kozanoglu et al. (2003)	✓	

Study	HCV infection described as 'chronic'	Test for HCV RNA
Maillefert et al. (2002)		✓
Mohammad et al. (2012)	✓	✓
Morasco et al. (2010)		✓
Narvaez et al. (2005)	✓	✓
Palazzi et al. (2008)		✓
Rieu et al. (2002)	✓	✓
Rivera et al. (1997)	✓	✓
Rivera et al. (1999)	✓	✓
Tsui et al. (2012)	✓	✓
Yucel et al. (2005)		✓

Of 15 studies describing HCV infection as chronic, only one explicitly defined what was meant by chronic HCV infection (Tsui et al. 2012: 3): 'defined as a positive HCV antibody result confirmed with detectable HCV RNA level on polymerase chain reaction (PCR) testing. Participants who were HCV antibody-positive and HCV RNA-negative were considered not to have chronic HCV infection (i.e. they had cleared their infection either spontaneously or through treatment).' Ten of the 15 studies describing HCV infection as chronic tested for the presence of HCV RNA.

In total, 16 of 26 studies tested for the presence of HCV RNA, of which eight provided findings in relation to pain outcomes for both anti-HCV and HCV RNA positivity, thus allowing a comparison of past and/or active infection with active infection (Calore et al. 2012, Goulding et al. 2001, Hsu et al. 2013, Maillefert et al. 2002, Narvaez et al. 2005, Palazzi et al. 2008, Rivera et al. 1997, 1999). Goulding et al. (2001) explicitly stated an intention to assess the effect that ongoing viral replication might have on symptomatology.

One of the 26 studies (Goulding et al. 2001) provided information regarding pain outcomes in patients with different durations of chronic infection.

Two studies assessed the association between viral load and pain or painful condition. Mohammad et al. (2012) examined the association between viral load and presence of FS. Morasco et al. (2010) examined the association between viral load and pain intensity as assessed by a numeric rating scale.

Buskila et al. (1997), De Vita et al. (2002) and Rieu et al. (2002) simply reported the proportion of participants with anti-HCV antibodies who were also positive for HCV RNA: 33, 91 and 76% respectively. Yucel et al. (2005) reported that a test for

HCV RNA positivity was conducted, but only appeared to present results in relation to anti-HCV positivity.

Route of infection

Only two of 26 studies examined a population of HCV-infected individuals, all of whom were likely to have been infected via medical intervention or contaminated blood products: Congia et al. (1996) and Yucel et al. (2005).

Ten of 26 studies provided no information regarding the likely route of HCV infection (Banks et al. 2007, Borque et al. 1991, Buskila et al. 1997, De Vita et al. 2002, Hsu et al. 2003, Kozanoglu et al. 2003, Maillefert et al. 2002, Narvaez et al. 2005, Palazzi et al. 2008, Rivera et al. 1999).

The proportion of HCV participants with a history of injection drug use was described in six studies: Barkhuizen et al. (1999) 43%; Goulding et al. (2001) 33%; Isaacs et al. (2013) 77.8%; Mohammad et al. (2012) 23%; Rieu et al. (2002) 33.3%; Tsui et al. (2012) 24%. Possible routes of HCV infection as described in the included studies are presented in Table 6.3.

Table 6.3: Association between HCV status and pain or painful conditions: studies describing possible routes of HCV infection (n = 26 studies).

Study	Possible routes of HCV infection
Baffoni et al. (1993)	The following were excluded: rheumatoid arthritis (RA) patients and controls with a proven or likely history of acute or chronic hepatitis, transfusion of blood products, IV drug use and haemodialysis, or with markers of liver damage.
Banks et al. (2007)	Not reported.
Barkhuizen et al. (1999)	121 HCV-positive patients: PWID 43%; transfusion 28%; tattoos 20%; promiscuity or seropositive partner 6%; occupational needle stick 4%; tissue graft 0.8%; no obvious exposure 21%; multiple possible exposures 21%.*
Borque et al. (1991)	Not reported.
Buskila et al. (1997)	Not reported.
Calore et al. (2012)	Sample roughly corresponds to a Vietnam era US veteran population likely to engage in high-risk behaviours.
Congia et al. (1996)	Transfusion-dependent thalassaemia patients.
D'Amico et al. (1996)	HCV-positive RA patients had no known risk factors such as PWID, acupuncture, blood transfusion, surgical intervention or endoscopic manoeuvre.

Study	Possible routes of HCV infection
De Vita et al. (2002)	Not reported.
Gharagozloo et al. (2001)	High frequency of HCV infection in haematologic malignancies could be attributed to frequent transfusion of patients due to suppression of haematopoiesis. Use of RA patients as a control group is signified by the fact that these patients require almost as frequent hospitalisation as patients with malignancies, which allows the authors to control to some extent for risk activities that might explain the acquisition of blood-born infection.
Goulding et al. (2001)	77 HCV-positive patients: contaminated anti-D immunoglobulin 64%, PWID 33%, transfusion 3.9%.
Guennoc et al. (2009)	Of 7 HCV-positive patients, 3 had previous surgery, of whom two also had had blood transfusions. A further 2 patients were born in areas with a higher prevalence of viral hepatitis (Vietnam and Togo).
Hsu et al. (2003)	Not reported.
Isaacs et al. (2013)	118 HCV-positive patients: PWID 41.9 %; blood transfusion 1.7%; homosexual 3.4%; heterosexual 0.9%; other 6%; unknown 46.2%.*
Kandemir et al. (2006)	Not reported.
Kozanoglu et al. (2003)	Not reported.
Maillefert et al. (2002)	Not reported.
Mohammad et al. (2012)	185 HCV-positive patients: blood transfusion 54%, of which the majority (80%) were infected through contaminated anti-D immunoglobulin; PWID 23%; neither 23%.
Morasco et al. (2010)	49 HCV-positive patients: 10.2% previous heroin use.
Narvaez et al. (2005)	Not reported.
Palazzi et al. (2008)	Not reported.
Rieu et al. (2002)	33 HCV-positive patients: 33.3% PWID; blood transfusion 9%; unknown 57.6%.
Rivera et al. (1997)	No statistically significant differences were found in past history of major surgery and blood transfusions or other

Study	Possible routes of HCV infection
	major organ involvement between patients with HCV-positive fibromyalgia and patients with HCV chronic hepatitis with less than seven tender points.
Rivera et al. (1999)	Not reported.
Tsui et al. (2012)	Injection drug use in past 6 months: HCV-positive patients 24%; HCV-negative patients 5%.
Yucel et al. (2005)	344 end-stage renal disease patients receiving regular haemodialysis therapy (109 HCV-positive).

*Multiple categories possible.

Liver disease status

The focus of this review is upon extrahepatic symptoms experienced by people with chronic hepatitis, but without liver failure. We have not included studies where the population under examination is composed entirely (or contains a majority of patients) with decompensated liver disease, advanced cirrhosis or liver failure. However, we have included studies where a spectrum of liver disease (from mild to severe) has been examined.

Disparity between comparison groups with regard to liver disease severity has not been used as an exclusion criterion in this synthesis because there is limited evidence to clarify the extent of liver damage required to influence hepato-metabolic function and its potential impact on extrahepatic pain outcomes.

Eight of the 26 included studies did not provide any information with regard to the liver disease status of patients and/or controls (Borque et al. 1991, Calore et al. 2012, De Vita et al. 2002, Gharagozloo et al. 2001, Hsu et al. 2003, Isaacs et al. 2013, Tsui et al. 2012, Yucel et al. 2005). The liver disease status of the patients in the 26 included studies is presented in Table A4.9 in Appendix 4.

6.3 Findings: arthralgia

Arthralgia, more commonly known as joint pain, can have many variants. Simple arthralgia presents with a main symptom of pain, but without inflammation in the joints or morning stiffness (Samanta et al. 2003).

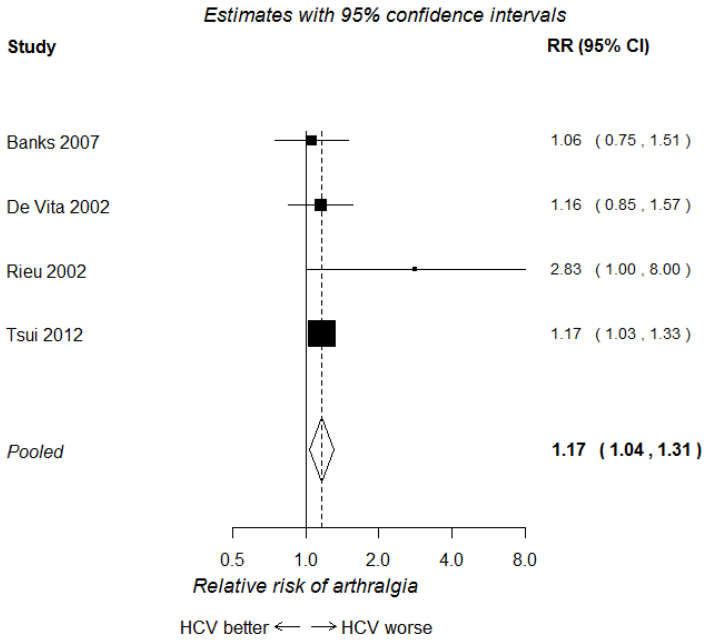
Of the seven studies examining the association between HCV infection and arthralgia, two (Banks et al. 2007, Tsui et al. 2012) were judged to be at moderate risk of bias. The key characteristics and findings of all seven studies are presented in Table A4.5 in Appendix 4.

Meta-analysis was based on four studies comparing arthralgia prevalence between people with and without HCV infection (Banks et al. 2007, De Vita et al. 2002, Rieu et al. 2002, Tsui et al. 2012).

Relative risks were pooled across studies using a DerSimonian-Laird random effects meta-analysis model. Heterogeneity was assessed using Higgins' I^2. As there were few studies in this meta-analysis, no meta-regressions were performed and funnel plot asymmetry was not assessed.

Figure 6.1 suggests that having HCV leads to a 17% increase in the prevalence of arthralgia. There was little heterogeneity across studies (I^2 = 8%).

Figure 6.1: Meta-analysis of the relative risk of arthralgia



Banks et al. (2007) found that 66.6% of 54 chronic HCV patients reported joint pain in comparison to 65.2% of 23 non-alcoholic fatty liver disease (NAFLD) patients (p = 0.90). The proportion of HCV and NAFLD patients reporting *inflammatory* joint pain was 36.1% and 40.0% respectively (p = 0.79). There was a disparity in smoking and alcohol history between the age groups, but the authors found no difference in the prevalence of these factors in those with or without joint pain (nor, contrary to expectation, BMI, weight, age and reports of depression or fatigue). The authors noted however, that NAFLD patients were more likely to be obese, which would predispose them to joint pain (the BMI of NAFLD patients was somewhat higher than those with HCV infection: 32.8 ± 2.11 versus 28.95 ± 1.93, p = 0.02). The extent of liver inflammation in the two patient groups was not assessed. While this study provides an opportunity to compare hepatitis patients with and without HCV virus infection, the NAFLD comparison group could be expected to have an elevated risk of joint pain due to weight status, and therefore any increased risk due to HCV infection in hepatitis patients might appear relatively low in this study. HCV-infected individuals were intended as the control group in this study, where the stated aim was to determine whether hepatic inflammation in general, despite causative aetiology, may lead to musculoskeletal complaints. The authors also noted that they did not pre-screen and exclude those with pre-existing joint complaints or diagnoses unrelated to liver disease.

De Vita et al. (2002) compared the presence of arthralgia/arthritis in a very small sample of HCV-positive (n = 12) compared to HCV-negative (n = 50) Sjögren's syndrome patients. Ten of 12 (83%) HCV-positive patients had arthralgia compared to 36 of 50 (72%) HCV-negative patients. Significant differences ($p < 0.05$) were observed in mean age (69 versus 56 years) between the two comparison groups, which may have resulted in a lowered risk of fibromyalgia in the younger, uninfected comparison group.

Rieu et al. (2002) examined the presence of arthralgia in a small sample of HCV-positive (n = 33) compared to HCV-negative (n = 14) symptomatic cryoglobulinaemia patients. The sociodemographic characteristics of the HCV-positive and -negative patients were not provided and therefore we were unable to judge if these groups were comparable. In addition, transaminases were significantly higher in the HCV-positive patients than in the HCV-negative patients (57.6% versus 14.3%, $p < 0.05$) indicating a disparity between groups in terms of liver disease.

Tsui et al. (2012) reported that 66% of 197 patients mono-infected with HIV had muscle or joint pain compared to 77% of 200 HIV-HCV co-infected patients ($p = 0.02$). In their final model using general estimating equations logistic regression analysis, the odds of muscle or joint pain was elevated amongst those co-infected with HCV, but just failed to reach statistical significance: OR 1.33, 95% CI: 0.98–1.81, $p = 0.07$. Before incorporating depressive symptoms into their model, the odds of muscle or joint pain among co-infected individuals were greater still: OR 1.45, 95% CI: 1.06–1.97, $p = 0.02$.

Whilst statistically non-significant, the results of Tsui et al. (2012) suggest that the odds of experiencing joint or muscle pain are greater for HIV-HCV co-infected than HIV mono-infected patients. However, it should be noted that the cohort of patients investigated all had alcohol problems (two or more affirmative responses to the CAGE alcohol screening questionnaire, or physician investigator diagnosis of alcoholism) and whilst groups were well balanced with respect to heavy alcohol use in the past six months, and adjustment was made for hazardous alcohol use in the analysis, severity of liver disease in each group was not reported.

The small number of studies in this meta-analysis (4 studies) did not allow for an examination of whether or not risk of bias (as estimated by the quality assessment tool) or co-morbidities (such as Sjögren's syndrome or symptomatic cryoglobulinaemia) are associated with a higher estimate of the risk of arthralgia in HCV-infected versus uninfected people. However, the low heterogeneity observed suggests that neither has an important influence.

Nevertheless, it should be acknowledged that the increased risk of arthralgia (17%) in those infected with HCV, as estimated in Figure 6.1, may be entirely due to confounding present in these observational studies. In addition, whilst all studies examined the outcome of arthralgia, the measure of arthralgia was different in each of the four studies and thus the severity of arthralgia under examination cannot be determined. For example, De Vita et al. (2002) specify only that arthralgia was determined via 'clinical evaluation' and Rieu et al. (2002) do not

specify whether arthralgia was assessed and reported by patients or clinicians. Therefore, despite the fact that we have two studies with moderate risk of bias whose findings meet the criterion for consistency (suggesting promising evidence of an increased risk of arthralgia in individuals with HCV infection), we do not give further consideration to the causal relationship between HCV infection and arthralgia in this report.

6.4 Findings: arthritis

Arthritis associated with HCV is most often described as 'rheumatoid like', with a majority of patients testing positive for rheumatoid factor - although there has been debate as to whether or not rheumatoid arthritis and HCV arthritis represent two distinct entities (Rosner et al. 2004). Typically, rheumatoid arthritis (in contrast to other forms of arthralgia) presents with at least four of these signs or symptoms for six weeks: pain and swelling in at least three joint areas; symmetrical presentation; early morning joint stiffness for more than one hour; involvement of metacarpophalangeal joints, proximal interphalangeal joints and wrists; subcutaneous nodules; positive rheumatoid factor and radiological evidence of erosions (Samanta et al. 2003).

Studies of arthritis were not included in a meta-analysis as it was not possible to compute appropriate effect size statistics in order to pool the results of these studies.

Of the eleven studies examining the association between HCV infection and arthritis, ten were at a high risk of bias and one was judged to be at a moderate risk of bias (Hsu et al. 2003) - we focus here upon the findings of this study. The key characteristics and findings of all eleven studies are presented in Table A4.6 in Appendix 4.

Using data from the US National Health and Nutrition Examination Survey (NHANES) III, Hsu et al. (2003) examined the possible association between hepatitis and rheumatoid arthritis (RA) in 4769 people aged ≥ 60 years. They found that those with *probable* RA had similar proportions with anti-HCV antibodies ($p = 0.32$) and HCV RNA ($p = 0.77$) to those without RA, as did those with *possible* RA (anti-HCV antibodies $p = 0.41$, HCV RNA $p = 0.92$). The relative odds of *probable* RA in relation to HCV serology, as estimated using design-based logistic regression adjusted for age, gender and race, found a negative but non-significant association in those positive for anti-HCV antibodies (AOR 0.44 95% CI: 0.07-2.80, $p = 0.37$) and those positive for HCV RNA (AOR 0.77, 95% CI: 0.10-6.19). Similarly, no significant association was found between *possible* RA and anti-HCV positivity (AOR 0.66, 95% CI: 0.20-2.15, $p = 0.48$) or HCV RNA positivity AOR 0.90, 95% CI 0.20-4.12). Whilst adjustment was made for age, gender and race, it should be noted that important confounders such as smoking, socio-economic status and liver disease severity were not considered in the analysis, and as a result, the findings of this study should be interpreted with caution.

This cross-sectional study also provided tentative evidence that there is no significant association between anti-HCV antibody/HCV RNA positivity and either probable or possible rheumatoid arthritis (Hsu et al. 2003).

The ten remaining studies examining the association between HCV infection and arthritis were found to be at high risk of bias (Baffoni et al. 1993, Borque et al. 1991, Congia et al. 1996, D'Amico et al. 1996, De Vita et al. 2002, Gharagozloo et al. 2001, Guennoc et al. 2009, Maillefert et al. 2002, Rivera et al. 1999, Yucel et al. 2005) - see Table A4.11 in Appendix 4.

The studies at high risk of bias provided a mixed and conflicting picture with respect to the relationship between HCV infection and arthritis.

Six studies examined the proportion of HCV-positive individuals among RA patients versus controls: Baffoni et al. (1993), Guennoc et al. (2009) and Maillefert et al. (2002) reported a lower proportion of HCV-positive individuals among RA patients, whereas Borque et al. (1991), D'Amico et al. (1996) and Rivera et al. (1999) found a higher proportion of HCV-positive individuals among RA patients - D'Amico et al. (1996) found this relationship to be statistically significant whereas Rivera et al. (1999) did not.

Two studies examined the proportion of individuals with RA (or RA and arthralgia) in HCV-positive individuals versus HCV-negative controls: both Congia et al. (1996) and De Vita et al. (2002) found a higher proportion of patients with RA in HCV-positive individuals, but despite the fact that De Vita et al. (2002) grouped patients with arthralgia and arthritis together in their analysis, only Congia et al. (1996) presented a statistically significant difference.

Yucel et al. (2005) performed a backward logistic regression analysis incorporating gender, age, duration of dialysis, cause of renal failure, hepatitis B infection, HCV infection and various laboratory parameters to determine the association between these factors and the prevalence of arthralgia in 284 of 344 chronic haemodialysis patients (32% anti-HCV-positive). They found 'a correlation' between arthralgia and anti-HCV positivity ($p < 0.001$).

Gharagozloo et al. (2001) compared the proportion of HCV-positive individuals amongst patients with various diseases, including RA, all of which may be caused by HCV infection.

It should be noted that simply counting the number of studies which reach statistical significance risks generating misleading findings by wrongly attributing 'no effect' findings to individual studies not sufficiently powered to detect a small, but clinically significant difference; it also ignores relative magnitudes of difference. Therefore, we do not present a narrative synthesis of the studies judged to be at high risk of bias and examining the relationship between HCV infection and arthritis. It is also important to note that four of these studies were conducted in Italy and two in Spain: both countries have a relatively high prevalence of HCV amongst their populations (Cornberg et al. 2011), and studies at

risk of selection bias and confounding are liable to produce spurious associations in regions where coincidental disease is more likely.

6.5 Findings: fibromyalgia syndrome

Fibromyalgia syndrome (FS), otherwise known as fibromyalgia, is a complex of symptoms including chronic widespread pain in combination with tenderness at 11 of 18 predictable anatomical sites known as tender points, often accompanied by fatigue, sleep disturbance and depression (Rahman et al. 2014).

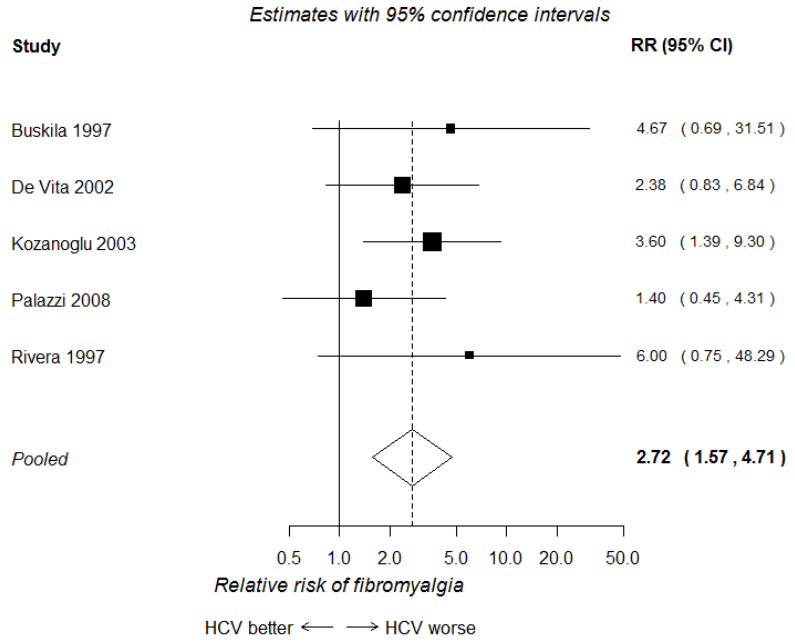
Of the nine studies examining the association between HCV infection and fibromyalgia, three were judged to be at moderate (as opposed to high) risk of bias (Buskila et al. 1997, Mohammad et al. 2012, Palazzi et al. 2008). The key characteristics and findings of all nine studies are presented in Table A4.7 in Appendix 4.

Meta-analysis was based on five studies comparing FS prevalence between people with and without HCV infection (Buskila et al. 1997, De Vita et al. 2002, Kozanoglu et al. 2003, Palazzi et al. 2008, Rivera et al. 1997).

Relative risks were pooled across studies using a DerSimonian-Laird random effects meta-analysis model. Heterogeneity was assessed using Higgins' I^2. As there were few studies in this meta-analysis, no meta-regressions were performed and funnel plot asymmetry was not assessed.

Figure 6.2 suggests that HCV infection is associated with a substantial increase in the prevalence of fibromyalgia. There was no heterogeneity across studies (I^2 = 0%).

Figure 6.2: Meta-analysis of the relative risk of fibromyalgia



Buskila et al. (1997) evaluated the prevalence of FS in a cross-sectional study of 90 patients with HCV, 128 healthy, anti-HCV-negative controls and 32 patients with non-HCV-related cirrhosis in Israel. They found a statistically significant difference in the prevalence of FS in HCV-positive individuals compared with healthy hospital personnel (15.5 versus 0%, $p < 0.001$) and patients with non-HCV-related cirrhosis (15.5% versus 3.1%, $p < 0.01$). The latter finding is incorporated in the meta-analysis. Although the severity of liver disease was not examined in HCV-positive patients versus non-HCV-related cirrhosis patients, an investigation of the prevalence of FS in HCV patients with varying degrees of liver damage revealed a statistically significant increase with increasing liver disease severity: 0%, 9.8% and 24.4% in HCV patients with no chronic liver disease, chronic hepatitis and cirrhosis respectively ($p < 0.08$). Nevertheless, fibromyalgia is known to be more prevalent among women, and the authors attributed the higher frequency of fibromyalgia in those with cirrhosis to the higher proportion of women with cirrhosis compared to chronic hepatitis: 68% versus 27% respectively.

De Vita et al. (2002) compared the presence of fibromyalgia in a small sample of HCV-positive (n = 12) compared to HCV-negative (n = 50) Sjögren's syndrome patients. Four of 12 (33%) HCV-positive patients had fibromyalgia compared to 7 of 50 (14%) HCV-negative patients. Significant differences ($p < 0.05$) were observed in mean age (69 versus 56 years) between the two comparison groups, which may have resulted in a comparatively lower risk of fibromyalgia in the younger, uninfected comparison group.

Kozanoglu et al. (2003) evaluated the presence of FS in 95 patients with chronic, untreated HCV infection and 95 healthy controls in Turkey. Fibromyalgia was found to be present in 18 (18.9%) of those with HCV infection and five (5.3%) healthy

hospital staff with no chronic disease history. Sociodemographic characteristics and confounders such as smoking status were not reported in each comparison group (other than age, gender and education).

Palazzi et al. (2008) conducted a case-control study to assess the prevalence of HCV infection in 152 Italian FS patients compared to 152 patients with non-HCV-related rheumatic degenerative disorders (peripheral osteoarthritis or sciatica due to L4-L5 or L5-S1 herniated disc). No statistically significant differences in anti-HCV antibody prevalence were detected between fibromyalgia patients and controls (4.6% versus 3.3%, p = 0.77).

Rivera et al. (1997) conducted both a case-control study of the prevalence of HCV infection in 122 FS patients in comparison with matched rheumatoid arthritis (RA) patients, and a cross-sectional study of the prevalence of FS in 58 chronic hepatitis patients attending a hospital hepatology unit compared with 58 age- and gender-matched patients attending a hospital general surgery unit. It should be noted however, that there is a possible association between RA and HCV infection. The cross-sectional study matched patients and controls for age and gender but did not report on other confounders with the potential to bias the findings. Six of 58 (10.3%) chronic HCV patients (five female) had fibromyalgia compared to one woman (1.72%) amongst the 58 general surgery controls (i.e. RR 6.0, 95% CI 0.75 – 48.29). The authors report p < 0.05 95% CI: -1.6 – 18.8 [sic].

Although Figure 6.2 indicates that having HCV leads to a substantial increase in the prevalence of fibromyalgia - with infected individuals appearing to be approximately 2.7 times more likely to experience fibromyalgia - studies with varying comparison groups have been included (e.g. healthy controls and chronically ill patients with osteoarthritis) and therefore it is not possible to quantify the increased risk attributable to HCV infection. It should also be noted that the included studies may be subject to confounding due to imbalances in sociodemographic and clinical factors between HCV-infected groups and control groups. Nevertheless, all five studies consistently showed an increased risk of fibromyalgia irrespective of type of comparison group. Since we have stipulated that at least four studies without a high risk of bias must be present to draw strong conclusions and only two of the five studies included in the meta-analysis have been judged to be satisfactory in terms of their methodological rigour (Buskila et al. 1997, Palazzi et al. 2008), the evidence supporting an association between HCV infection and increased risk of fibromyalgia may only be described as ‘promising’.

A meta-analysis of five studies comparing fibromyalgia prevalence between people with and without HCV infection provides promising evidence to suggest that HCV infection is associated with a higher prevalence of fibromyalgia irrespective of the co-morbidities of those with HCV infection or the health status of the comparison group.

The small number of studies in this meta-analysis (5 studies) did not allow for an examination of whether or not risk of bias (as estimated by the quality assessment tool), or co-morbidities (such as Sjögren's syndrome), were associated with a higher

estimate of the risk of fibromyalgia in HCV-infected versus uninfected people. However, there was no heterogeneity across studies ($I^2 = 0$).

One further study at moderate risk of bias was located which examined the association between HCV infection and fibromyalgia (Mohammad et al. 2012), but was not included in the meta-analysis as it did not report the prevalence of fibromyalgia between those with and without HCV infection.

Mohammad et al. (2012) examined the prevalence of FS in a cross-sectional study of 185 Irish patients with chronic HCV, using univariate logistic regression analysis to determine the risk factors independently associated with FS, including route of acquisition of the virus, viral genotype and viral load. Female gender, age ≥ 45 years, acquisition of HCV through blood transfusion and infection with HCV genotype 1 were independently associated with the presence of FS ($p < 0.001$). No significant association was found between FS and viral load ($p = 0.174$). The authors note the lack of data on liver biopsy and the extent of liver cirrhosis as a limitation of the study, but state that 'previous studies have not reported a link between FS and the degree of hepatic necrosis and inflammation' (Mohammad et al. 2012: 410).

Fibromyalgia and patients infected via contaminated blood products

Three studies presented findings in relation to route of infection and fibromyalgia syndrome (Goulding et al. 2001, Mohammad et al. 2012, Rivera et al. 1997). Of these three studies, just one (Mohammad et al. 2012), was judged to be at moderate (as opposed to high) risk of bias.

Mohammad et al. (2012) used univariate logistic regression analysis to show that acquisition of HCV through blood transfusion was independently associated with the presence of FS in 106 subjects with chronic HCV infection ($p < 0.05$). Of these, 65% had acquired HCV via blood transfusion compared to 35% of 44 chronic HCV patients without fibromyalgia syndrome ($p < 0.001$).

Therefore, one study at moderate risk of bias provided evidence to suggest that acquisition of HCV through blood transfusion was independently associated with the presence of FS in 106 patients with chronic HCV infection.

The two remaining studies examining the association between the route of HCV infection and fibromyalgia outcomes were found to be at high risk of bias (Goulding et al. 2001, Rivera et al. 1997) - see Table A4.7 in Appendix 4.

Conjectural mechanisms through which HCV infection may induce fibromyalgia as proposed by the authors of included studies

Buskila et al. (1997) note that little is known regarding the pathogenesis of FS, but identify a number of studies providing evidence that infectious agents may trigger a cascade of factors, such as abnormal levels of neurohormones and growth factors promoting the chronic musculoskeletal pain, fatigue and sleep disturbance characteristic of fibromyalgia. Kozanoglu et al. (2003) also report that the exact mechanism through which chronic viral hepatitis causes extrahepatic manifestations is unclear, but may be mediated by immune mechanisms, release of

cytokines such as interleukin-8 or deficiency of insulin-like growth factor. However, in common with Goulding et al. (2001), they cite research conducted by Goldenberg (1993), which proposes that anxiety caused by chronic infection may lead to a changed behaviour pattern featuring sleep disturbance and decreased physical activity.

Whilst remarking that the 'pathophysiology of fibromyalgia is uncertain', Goulding et al. (2001) discuss a possible mechanism for HCV-induced extrahepatic manifestations involving lymphocyte activation and subsequent cytokine release. Goulding and colleagues suggest that the significant difference in tender point value (2.48) for injection drug users (where mean duration of infection was 10 years) as opposed to the mean tender point value (5.0) for those infected by contaminated anti-D immunoglobulin (where mean duration of infection was 21 years) could reflect a shorter exposure to ongoing lymphocyte activation. However, since the authors failed to find a difference in mean tender point values between HCV-positive patients with and without ongoing viral replication (as assessed by PCR-positive serology), they conclude that the duration of disease is unlikely to be a factor (Goulding et al. 2001: p510).

In particular, it is worth noting that Goulding et al. (2001) found that all fibromyalgia patients were infected via contaminated blood products, were female, and had high anxiety and depression scores. Taken together with the fact that fibromyalgia occurred in both PCR-positive and PCR-negative patients they suggest that it could be: 'the trauma or stress related to the diagnosis of HCV in this particular group that is most central to the diagnosis of fibromyalgia' (Goulding et al. 2001: p510).

Mohammad et al. (2012) state that there are 'no compelling data to suggest a causal relationship' between HCV infection and fibromyalgia syndrome, but also suggest that psychological distress and the diagnosis of HCV infection per se may result in a significant reduction in physical function.

Similarly, whilst noting, as do Buskila et al. (1997), that the development of fibromyalgia is more frequent in patients infected with viruses such as HIV, Palazzi et al. (2008: p102) also suggest that the 'awareness of having a chronic disease with a possible severe evolution could play an important role in the development of fibromyalgia'.

No further studies were retrieved in the search which either tested the plausibility of a relationship between HCV infection and fibromyalgia by studying a proposed biological mechanism, or which evaluated biological markers of fibromyalgia in those with HCV infection.

6.6 Findings: miscellaneous pain outcomes

Of the three studies examining the association between HCV infection and miscellaneous pain outcomes, one was judged to be at moderate (as opposed to high) risk of bias (Morasco et al. 2010) - we focus here upon the findings of this study. Key characteristics and findings of all three studies are presented in Table A4.8 in Appendix 4.

Morasco et al. (2010) investigated the association between pain intensity (as assessed on a numeric rating scale) and viral load in a sample of 49 HCV-positive US veterans. Correlation coefficients were developed to examine the associations among variables of interest. Hierarchical multiple regression analyses were conducted to evaluate variables associated with pain outcomes: demographic variables (age and BMI) were entered in step 1, disease and treatment-related variables (viral load, liver disease severity, prescribed opioid medication) were entered in step 2, and psychological variables (severity of depressed mood and substance dependence severity) were entered in step 3. Only step 3, with the psychosocial variables included, was significant ($p = 0.002$) and accounted for 20.9% of the unique variance in pain intensity. The only independent predictor of pain intensity was depression severity ($\beta = 0\ .483$, $p < 0.001$).

It should be noted that the sample size in this study is relatively small ($n = 49$) and composed entirely of US veterans (approximately 10% of whom had a history of heroin use) thus limiting generalisability to other populations. Thus there is tentative evidence that there is no significant association between viral load and pain intensity.

The two remaining studies examining the association between HCV infection and pain outcomes were found to be at high risk of bias (Barkhuizen et al. 1999, Isaacs et al. 2013) – see Table A4.13 in Appendix 4.

6.7 Findings: association between pain outcomes and route of infection

Four of 26 studies provided results regarding extrahepatic pain in patients with varying routes of infection (Barkhuizen et al. 1999, Goulding et al. 2001, Mohammad et al. 2012, Rivera et al. 1997). Of these four studies, one (Mohammad et al. 2012) was judged to be at moderate (as opposed to high) risk of bias.

Barkhuizen et al. (1999) found that HCV-infected patients with a history of injection drug use (35% of 52 patients) or tattoos (38% of 24 patients) were slightly more likely to have *diffuse* pain than those with blood product exposure (18% of 34 patients), but this did not reach statistical significance. Similarly, patients with a history of injection drug use (90% of 52 patients) or tattoos (96% of 24 patients) were slightly more likely to have *musculoskeletal* pain than those with blood product exposure (82% of 34 patients), but this did not reach statistical significance either. This study was judged to be at high risk of bias and the results should therefore be considered potentially misleading.

Goulding et al. (2001) found a mean number of tender points of 5.0 in 49 patients infected via contaminated anti-D immunoglobulin, which was significantly higher than a mean of 2.8 tender points in 25 age- and gender-matched controls ($p = 0.03$) and a mean of 2.48 tender points in injection drug users ($p < 0.01$). This study was judged to be at high risk of bias and the results should therefore be considered potentially misleading.

Mohammad et al. (2012) used univariate logistic regression analysis to show that acquisition of HCV through blood transfusion was independently associated with the presence of fibromyalgia syndrome (FS) in 106 subjects with chronic HCV infection

($p < 0.05$). Of those patients, 65% had acquired HCV via blood transfusion compared to 35% of 44 chronic HCV patients without FS ($p < 0.001$).

Rivera et al. (1997) reported that 'no statistically significant differences were found in past history of major surgery and blood transfusions or other major organ involvement between patients with HCV-positive fibromyalgia and patients with chronic hepatitis with less than seven tender points.' This study was judged to be at high risk of bias and the results should therefore be considered potentially misleading.

Thus these four studies failed to provide a consistent picture with regard to route of infection and pain or painful conditions, although one study at moderate risk of bias provided tentative evidence to suggest that acquisition of HCV through blood transfusion was independently associated with the presence of FS.

6.8 Findings: association between pain outcomes and liver disease status

Four of 26 studies provided results regarding extrahepatic pain in patients with varying degrees of liver disease severity (Banks et al. 2007, Barkhuizen et al. 1999, Buskila et al. 1997, Morasco et al. 2010). Of these four studies, three were judged to be at moderate risk of bias (Banks et al. 2007, Buskila et al. 1997, Morasco et al. 2010) and one at high risk of bias (Barkhuizen et al. 1999).

The four studies examined different extrahepatic pain outcomes (joint pain, musculoskeletal pain, presence of fibromyalgia and pain intensity) in patients with varying degrees of liver disease severity. Each of the individual studies with a moderate risk of bias (n=3) failed to demonstrate a relationship between severity of liver disease and extrahepatic pain or painful conditions.

Banks et al. (2007) used liver histology results from biopsy of each subject, including amount of fibrosis and Knodell score, as an indicator of the severity of liver disease (amount of hepatic inflammation seen). In a logistic regression, the extent of fibrosis and Knodell score were not found to be associated with joint pain.

Barkhuizen et al. (1999) found no statistically significant association between musculoskeletal pain and liver disease severity in a subset of 90 HCV-positive patients with liver biopsies available. Musculoskeletal pain was present in 87% of 69 severe liver disease patients versus 67% of 21 mild-to-moderate disease patients ($p > 0.05$), and 64% of 47 cirrhosis patients versus 46% of 43 patients without cirrhosis ($p > 0.05$). However, this study was judged to be at high risk of bias and the results should therefore be considered potentially misleading.

Buskila et al. (1997) investigated the prevalence of FS in HCV patients with varying degrees of liver damage and found a statistically significant increase with increasing liver disease severity: 0%, 9.8% and 24.4% in HCV patients with no chronic liver disease, chronic hepatitis and cirrhosis respectively ($p < 0.08$). However, fibromyalgia is known to be more prevalent among women (Branco et al. 2010), and the authors attributed the higher frequency of fibromyalgia in those

with cirrhosis to the higher proportion of women in the group with cirrhosis compared to chronic hepatitis: 68% versus 27% respectively.

As described in Section 6.6, Morasco et al. (2010) did not find liver disease to be an independent predictor of pain.

6.9 Discussion

This analysis sought to examine whether chronic HCV infection was associated with pain and painful conditions, and the strength of this relationship in people living with HCV. The findings of 26 studies on pain and pain-related conditions were considered.

We found promising evidence that being infected with HCV is associated with an increase in the prevalence of fibromyalgia and arthralgia, although it is possible that the observed results may be due to confounding. Evidence regarding an association between HCV and arthritis is tentative but indicates no association.

In general, the quality of the evidence available to assess the association between chronic HCV infection and pain was poor. No studies were found to be at low risk of bias. In particular, most of the research available did not address factors which might also account for the association between HCV infection and pain outcomes such as socio-economic status or smoking - both of which are known risk factors for painful outcomes (Di Giuseppe et al. 2014, Kvalheim et al. 2013). Only five of the 26 studies gave consideration to confounding factors in their analyses. In addition, the majority of the included studies were cross-sectional or case-control studies unable to provide information regarding whether or not painful symptoms or conditions occurred prior to infection with HCV.

In terms of identifying which groups of people with chronic HCV are affected by extrahepatic conditions, previous research has found that factors such as advanced age and gender are risk factors for clinical and biologic extrahepatic manifestations (Cacoub et al. 1999). Unfortunately, the included studies did not support an investigation of which groups of individuals with chronic HCV infection are affected by extrahepatic pain or painful conditions. It should be noted however, that two of the three painful conditions investigated in this review (rheumatoid arthritis and fibromyalgia), manifest predominantly in women (Branco et al. 2010, National Institute for Health and Care Excellence 2013). One study at moderate risk of bias provided evidence to suggest that acquisition of HCV through blood transfusion was independently associated with the presence of fibromyalgia syndrome in patients with chronic HCV infection (Mohammad et al. 2012). The available evidence failed to demonstrate a significant relationship between extrahepatic pain and the severity of liver disease in patients, i.e., it appeared that pain was not conditional upon liver damage.

It was not possible to accurately determine the relationship between HCV infection and risk of arthritis; only tentative conclusions can be drawn. And although meta-analyses of evidence regarding prevalence of fibromyalgia and arthralgia provides promising evidence of an association with HCV, larger, longer-term prospective studies with sufficient power and follow-up to determine the association between

HCV and pain or painful conditions would help to provide more robust evidence. An association is necessary to establish causality, but it is not in itself sufficient. Confounding may have been entirely responsible for the observed association between HCV infection and arthralgia, added to which, measures of arthralgia were inconsistent across studies. Evidence for a lack of association between HCV infection and arthritis was tentative. Therefore, we have not given further consideration to the putative relationship between HCV infection and arthralgia or arthritis in this report. More robust evidence with respect to possible biological mechanisms would help to clarify whether or not HCV is a causative agent of fibromyalgia. With regard to the aetiology of fibromyalgia, a dose-response relationship was examined in one study at moderate risk of bias (Mohammad et al. 1012), but failed to find a significant association between fibromyalgia and viral load ($p = 0.174$). One study with a high risk of bias (Goulding et al. 2001) provided evidence to suggest that duration of infection may provide an explanation for the increased pain experienced by those infected via contaminated blood products compared to those infected via unsterile drug injecting practices; however, the findings demonstrated no statistically significant difference in tender points between those with ongoing viral replication as opposed to those with no viral replication, a scenario inconsistent with this hypothesis.

7. Discussion

7.1 Main findings

Overall, the findings from this systematic review suggest that HCV is associated with poorer quality of life and increases in depression, anxiety and the pain conditions fibromyalgia and arthralgia. The evidence base in not well developed for our review's research questions; lack of equivalence between HCV and comparison groups was a common feature, such that individual findings are graded as 'promising' or 'tentative' rather than 'strong'.

A total of 29 studies examining the relationship between HCV and quality of life met our inclusion criteria. Twenty-two studies provide promising evidence that people with HCV have worse quality of life than 'general' or 'healthy' populations. Meta-analysis of nine studies showed both physical and mental domains of quality of life to be significantly worse among people with HCV compared to people without HCV (PCS: MD 5.54, 95% CI 3.73-7.35, MCS: MD 3.81, 95% CI 1.97-5.64). Quality of life was reduced in both HCV patients with an iatrogenic infection and HCV patients with a non-iatrogenic infection when compared to those without HCV; the deficit appeared to be of a similar magnitude in both types of HCV groups. Seven studies provided promising evidence to indicate that people who were co-infected with HCV and HIV had worse quality of life than people infected with HIV alone. Meta-analysis of five studies indicated that both the physical and mental health domains of quality of life were significantly worse among people who were co-infected (PCS: MD 2.57, 95% CI 1.08-4.06, MCS: MD 1.88, 95% CI 0.06-3.69).

Findings were drawn from 22 studies examining the association between HCV and depression and anxiety. Evidence indicates that depression and anxiety are more severe, and depression is more common among people with HCV compared to people without HCV. Meta-analysis of 12 studies provided promising evidence that the severity of depression in people with HCV is significantly greater than among those without HCV (MD 0.98, 95% CI 0.43-1.53). Meta-analysis of nine studies provided promising evidence that the severity of clinical anxiety is significantly greater among people with HCV (MD 0.47, 95% CI 0.09-0.86). Meta-analysis of seven studies provided promising evidence that participants with HCV are approximately three times more likely to be depressed compared to those without HCV (OR 2.77, 95% CI 1.62-4.74). No statistically significant evidence that anxiety is more common among people with HCV was found. Similarly, incidence of depression is more likely among people co-infected with HCV and HIV, compared to those infected with HIV only (OR 2.15, 95% CI 1.37-3.37); however, there was no evidence to suggest that the severity of depression or anxiety was higher in co-infected groups compared to HIV-only groups.

Findings from 26 studies with high or moderate risk of bias on the association between pain and HCV were examined. We found promising evidence that being infected with HCV is associated with an increase in the prevalence of fibromyalgia and arthralgia. Evidence examining HCV and arthritis indicates no association, but

this finding is tentative. A meta-analysis of four studies comparing arthralgia prevalence between people with and without HCV infection suggested that being infected with HCV is associated with a 17% increase in the prevalence of arthralgia (RR 1.17, 95% CI 1.04-1.31). However, it is possible that the observed results may be due to confounding in the observational studies examined. A meta-analysis of five studies suggested that people with HCV are significantly more likely to suffer from fibromyalgia. However, key differences across the studies in terms of the health status (co-morbidities) of HCV patients and comparison groups mean it is not possible to quantify the increased risk attributable to HCV infection. Other studies were not amenable to meta-analysis and studies with high risk of bias were not considered in narrative analyses. Available evidence from just one suitable study with a moderate risk of bias showed no significant association between arthritis and HCV. Three studies with a moderate risk of bias examined different extrahepatic pain outcomes (joint pain, presence of fibromyalgia and pain intensity) in patients with varying degrees of liver disease severity. Here, each of the individual studies failed to demonstrate a relationship between severity of liver disease and extrahepatic pain or painful conditions. And whilst statistically non-significant, the results of one located study where participants were heavy users of alcohol suggested that the odds of experiencing joint or muscle pain are greater for people co-infected by HIV and HCV when compared with those for people infected with HIV alone.

In addition to the in-depth syntheses of depression, anxiety, pain and quality of life, we mapped the epidemiological literature examining the relationships between HCV and extrahepatic conditions. This found that 194 extrahepatic conditions had been studied as potentially associated with HCV, of which diabetes, non-Hodgkin's lymphoma, mixed cryoglobulinaemia, depression, cognitive dysfunction, insulin resistance and lichen planus were the most frequently researched. Depression, anxiety and painful conditions were identified by representatives from HCV advocacy groups as a priority for examination in our review; however the map identified systematic reviews and/or primary studies for each of the other extrahepatic conditions, which could be examined in detail if deemed a future research need.

7.2 Prioritising extrahepatic conditions

Several sources were examined to determine which extrahepatic conditions might be the most 'important'. As part of this, consultations within this review presented differing stakeholder perspectives on the most relevant focus of scientific research examining HCV, extrahepatic conditions and quality of life.

The findings of this review indicate a level of concordance between the focus of scientific research and the conditions identified as most pertinent to people living with HCV as identified by advocacy group representatives.

While the literature identified a focus on range of medical conditions, such as diabetes, cardiovascular conditions and autoimmune disorders, it also focused on a range of neurological conditions, such as depression, anxiety, pain, cognitive function and fatigue, that members of patient advocate groups identified as key

conditions that impact on the quality of life of people with HCV. In fact, the associations between HCV and neurological conditions were the most frequently researched. However there appears to be a mismatch with regard to the issue of painful conditions which was the eighth most commonly researched condition type in our map. The extrahepatic conditions identified as important by advocacy group members also differed from those of interest to some members of our Scientific Advisory Group.

The brief examination of the National Hepatitis C Register that we were able to undertake provided some promising insights into future research examining longitudinal data from those iatrogenically infected with HCV; this offers a promising way to understand morbidity and mortality in the population most relevant to this review.

It should also be considered that the patient advocacy groups do not necessarily represent all of the population of interest. It could be that the majority of those iatrogenically infected with HCV are experiencing other extrahepatic conditions which are impacting on their quality of life. Short of undertaking a survey of all known iatrogenically infected people, the National Hepatitis C Register is the closest source of prospectively-collected data available which may answer the question of which extrahepatic conditions are associated with morbidity and mortality in this population.

There is an apparent set of links between HCV, depression, anxiety and quality of life that merits further research and consideration by professionals working with people infected with HCV and potential HCV patients, e.g. counsellors might recognise the potential for increased support to cope with these extrahepatic conditions and tailor advice and referrals accordingly.

The studies included in these syntheses did not describe consistently their participants' route of HCV infection, and very few studies examined relationships in 100% iatrogenically infected people. This makes it difficult to separate out associations which might be due to HCV infection alone from associations which might be due to factors related to route of infection.

7.3 Strengths of our review

One of the key strengths of this review is that it is tailored to the needs of HCV patients themselves; consultation with advocacy group representatives identified the conditions which they consider have the most significant impact on the lives of people with HCV, as opposed to what is easily diagnosable, treatable or pathologically interesting. Another strength is that it represents the most comprehensive effort within a systematic review to date to consider the issue of confounding bias. Whilst we were not able to fully eradicate this potential bias, we were able to take steps to reduce the susceptibility of our findings to it, and to grade the strength of the evidence accordingly. Furthermore, this is the most comprehensive systematic review we are aware of that addresses the needs of specific groups of people with HCV. First as this review focuses specifically on HCV patients without cirrhosis, it provides particularly useful findings for policy makers

and those with HCV in the UK since the majority of patients not currently registered by the Skipton Fund[1] are non-cirrhotic. Second, in-depth examination of the impact of extrahepatic conditions and quality of life specifically in HCV-HIV co-infected groups provides valuable evidence regarding another key group of HCV patients.

7.4 Limitations of the evidence

There are some limitations to the primary studies included in our review, which should be considered. All of the primary research we located was judged to be at moderate or high risk of methodological bias for the purposes of our review's research questions; a common feature was lack of appropriate comparison groups or accounting for confounding variables. In observational studies, confounding is often responsible for a spurious association (or lack of association) being found between exposure (in this case HCV infection) and outcome (in this case quality of life, or EHCs). Comparison groups must be very carefully selected and matched, and information about potential confounding factors precisely measured for both exposed and unexposed groups, such that their effect on the association can be taken into account during analysis. A general lack of attention to these issues across the studies limited our ability to assess the evidence of the causal role of HCV in quality of life, depression, anxiety and pain, as the findings may be the result of other factors (such as PWID) influencing the study's findings. Particularly with respect to controlling for other factors that might also explain any relationships, not controlling for or analysing by route of HCV infection (e.g. PWID) was the most common confounder across studies. In addition, advanced age and gender are risk factors for clinical and biologic extrahepatic manifestations (Cacoub et al. 1999).

Across topics studied in the in-depth syntheses, comparison groups were of questionable equivalence: several studies utilised family members, hospital staff and unknown 'community members' to compare to HCV patients. While family members were probably similar to HCV patients in terms of socio-economic status, they and hospital staff and community members could have been systematically different from HCV patients on important confounders, such as injection drug use, education or employment status, which were not routinely measured and/or reported.

All studies included in the analyses were cross-sectional in terms of their design, i.e. they only measured associations at one point in time. We had hoped to locate a pool of studies that were prospective in nature, of large samples of participants with information on their route of infection recorded and analysed separately. A collection of studies with these design features would have provided more rigorous findings about causality. The studies we did locate can only tell us about association and point to suggested pathways of exploring causality in future.

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[1] The Skipton Fund registers people iatrogenically infected with HCV.

Very few studies included in the syntheses examined extrahepatic associations in those who spontaneously cleared HCV. Some literature has suggested that extrahepatic conditions may be experienced by those who spontaneously clear the HCV virus (Barrett et al. 2001). This may merit further examination, as it is a question relevant to those who have acquired HCV through blood products. Importantly, despite frequent measurement of HCV by RNA polymerase chain reaction, the studies did not usually differentiate between HCV patients who had naturally cleared the disease and those who were currently viraemic, and this would seem an important area for further examination.

This set of included studies also revealed little about the impact of liver disease progression on extrahepatic conditions, as few studies conducted or reported analyses by liver disease severity.

Finally, we note that there was a lack of high-quality UK-based studies available, with a single UK-based study included in each of the quality of life (Foster et al. 1998) and pain (Isaacs et al. 2013) syntheses, and no UK-based studies included in the depression and anxiety synthesis. Two multinational studies on quality of life included UK samples, but these studies did not provide UK-specific findings (Vietri et al. 2013, Ware et al. 1999).

7.5 Limitations of our review

We found that 194 EHCs had been studied as possibly associated with HCV infection. A systematic examination of the literature for all of these possible associations would take several years. Our map of the literature, despite being systematic, can only indicate the kinds of research that have been conducted and should not be taken as an indication of actual extra hepatic conditions.

Due to the timeline required for this review, we were not able to examine studies prioritised by the patient advocacy groups on the relationships between HCV and cognitive function and HCV and fatigue, although these studies are readily available for future synthesis. Our map identified other bodies of literature that may be judged important for full analysis. Diabetes, for example, may have a significant burden from a patient's perspective and in terms of morbidity and mortality (White et al. 2008).

The National Hepatitis C Register was briefly assessed as a potential source of information. This database was established in 1998 in order to track the natural history of HCV infection in UK patients. It contains anonymised data of, amongst others, patients who acquired HCV by transfusion. This source was identified late in the review process and its information could not be fully integrated within the timeframe of this project, as it would require the design and implementation of a robust research study in order to get a reliable answer. However, as some questions potentially refer to extrahepatic conditions, this register is a key source to understand significant morbidity and mortality in iatrogenically infected patients living with HCV.

Lastly, systematic reviews can benefit from the parallel inclusion and synthesis of other types and sources of evidence which can help to explain the apparent

relationships identified between HCV and quality of life, pain, depression and anxiety. For example, a review of robust research examining potential biological mechanisms may help to establish causality, or a synthesis of qualitative research examining the experiences of people with HCV may help to unpack the ways in which HCV impacts on people's quality of life or leads to depression and anxiety. Furthermore, whilst the focus on the association of HCV with quality of life and extrahepatic conditions is both an important and essential first step in addressing the problem, it falls short of being able to identify the most appropriate intervention approaches to prevent or alleviate the detrimental impacts of HCV.

7.6 Evidence gaps

Some specific gaps in the research evidence have been identified from the review. First, the included studies are only measuring association, not causation; thus we cannot infer that HCV 'causes' depression, anxiety, pain or lower quality of life, only that the two tend to be seen together. For example, it is possible that people who are depressed tend to inject drugs, putting them at risk of HCV. Cross-sectional research designs do not adequately establish causation. **To be able to adequately assess causation, longitudinal research with adequate power and sufficient follow-up examining the relationship between HCV and extrahepatic conditions needs to be undertaken.**

Assessing causation was not possible in this dataset, in part due to the poor reporting of other factors related to HCV which could also have affected the relationships with depression, anxiety, pain and quality of life. **Future research needs to adequately measure, report, adjust for and analyse separately (where appropriate) all data for both sample and comparison groups on important potential confounding factors, including route and duration of infection, liver disease severity, age, gender, education, socio-economic status and current injection drug and alcohol use. Designs utilising appropriate comparison groups should be employed, matching or adjusting for non-equivalence.**

We found limited UK research on these associations, and little on iatrogenically infected populations in particular. **To understand the relationships between HCV and extrahepatic conditions in iatrogenically infected populations, UK-based research with these people needs to be conducted.**

This review identified little research on HCV-HIV co-infected groups. **To understand the impact of extrahepatic conditions on HCV-HIV co-infected groups, primary research on this group needs to be undertaken.**

Some studies of extrahepatic conditions may have been undertaken prior to 1991, when many people who received blood transfusions were infected with HCV but before the HCV virus was identified. They may be of sufficient rigour to include in future syntheses. **This could be ascertained by searching and screening a random sample of studies published before 1991 to determine whether they would meet inclusion criteria.**

These studies did not further differentiate between HCV patients who had naturally cleared the disease and those who were currently viraemic. We note that 'mono'-

infected does not differentiate between those who spontaneously cleared the virus without treatment, those who cleared the treatment and those who did not clear with treatment. The association with depression and/or anxiety in this set of studies may differ, but this cannot be established from this set of studies. **This suggests a need to examine the relationship between extrahepatic conditions and/or quality of life in patients who have cleared HCV spontaneously as well as those who have undergone treatment, to determine whether the prevalence of extrahepatic conditions is similar.**

Studies also revealed little about the impact of liver disease progression on extrahepatic conditions, as few studies conducted or reported analyses by liver disease severity. **To understand whether extrahepatic conditions and quality of life change with liver disease severity, future research reporting and analysing by liver disease severity is warranted.**

Diabetes, non-Hodgkins' lymphoma, mixed cryoglobulinaemia, cognitive function, insulin resistance and lichen planus were most frequently researched and have a mix of systematic reviews and primary studies; cognitive function and fatigue were identified as priority extrahepatic conditions by advocacy group members but were not synthesised. **Future syntheses of these extrahepatic conditions could be undertaken as policy need arises.**

This is the most comprehensive systematic review in the area; yet we have not been able to examine all potentially associated extrahepatic conditions. A body of literature examining associations between HCV and over 190 different extrahepatic conditions has been identified, with relatively few systematic reviews conducted in the area. This indicates a current need in evidence synthesis. **There is a need for a programme of evidence mapping to more fully describe and so identify the full potential for the literature that explores associations between HCV and extrahepatic conditions in general.**

As it is currently the best representation of the population of interest, a prospective study of the National Hepatitis C Register should be developed, in order to understand morbidity and mortality related to extrahepatic conditions. The findings from this study could be used to design and conduct a new systematic review on the relevant extrahepatic conditions, using the studies identified in this review.

Most included studies utilised inappropriate comparison groups, many of whom were not equivalent to HCV samples. People who have acquired HCV through blood transfusions have a pre-existing underlying morbidity (such as haemophilia or cancer) which necessitated blood transfusions. **To understand a true association between HCV and extrahepatic conditions in iatrogenically infected groups, a longitudinal study should be undertaken comparing the prevalence of extrahepatic complications in patients who acquired HCV from a blood or blood product transfusion against age- and gender-matched groups who were also transfused but did not acquire HCV infection.**

7.7 Answering the review's research questions

In conclusion, the review addressed the overarching research questions in the following ways:

1. In general, how is chronic HCV infection associated with health-related quality of life?

   The findings from this review of studies at high and moderate risk of bias in their conduct and design suggest that HCV infection is associated with depression, anxiety, fibromyalgia, arthralgia and lower quality of life in HCV-positive patients compared to uninfected groups, and with lower quality of life in HCV-HIV co-infected patients compared to HIV-infected patients.

2. Which extrahepatic conditions are associated with chronic HCV infection?

   While studies of the possible association of HCV with 194 different extrahepatic conditions were identified, we examined associations identified by advocacy group representatives as being of high priority to people living with HCV: depression, anxiety and pain.

3. What is the strength of the relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?

   Again, time constraints meant that we were unable to assess the strength of the relationship between depression, anxiety and pain and quality of life in HCV patients, although some literature was identified which could be synthesised in future.

4. Which groups of people with chronic HCV are affected by extrahepatic conditions? Are there any moderating factors (e.g. age, gender, co-morbidity, iatrogenic acquisition, ethnicity, lifestyle risks) that influence the strength of any relationship between extrahepatic conditions and health-related quality of life in people living with chronic HCV?

and

5. Are there any mediating factors (e.g., co-morbidity, socio-economic factors, lifestyle factors) that might explain any observed significant relationship between extrahepatic conditions and health-related quality of life?

   Some evidence was identified which suggested that women infected with HCV were more likely to experience fibromyalgia. Sub-group analyses of iatrogenic acquisition did not indicate differences in associations of depression, anxiety, pain or quality of life. No other moderating or mediating factors were identified; these were poorly reported overall.

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Section II. Technical description of the review

9. Detailed review methods

9.1 Advisory Group, advocacy group consultations and assessment of the National Hepatitis C Register

The perspectives of various stakeholder groups informed the scope of the review. We consulted key experts, including The UK National Health Service and Department of Health Health Policy Advisers, epidemiologists, virologists, hepatologists and representatives from advocacy groups in order to obtain their views in one of two ways. An Advisory Group of key experts was assembled, with the role of: helping to identify relevant datasets and studies for analysis; providing contextual understanding of extrahepatic conditions related to HCV; advising on the review's research questions; helping to focus the scope of the review in order to determine which studies to include in the analysis; and commenting on initial findings and the final report. Advisory Group members were invited to comment on the draft protocol by email and to attend a face-to-face meeting in early February 2014 to discuss the initial findings of screening and coding references and to identify a topic on which to focus for in-depth review synthesis. They were also contacted by email with the draft findings so that they could comment on them and help to produce relevant recommendations for policy and practice. To ensure a balance of stakeholders, the Advisory Group included professionals well-networked with their peers and advocacy groups, such as The British Liver Trust and the Hepatitis C Trust, who were well connected to people affected by HCV.

It was also recognised that other advocacy groups which were smaller, or whose interest in HCV was not their main focus, might also usefully inform the review. In order to ensure that a wide range of stakeholders had an opportunity to provide their views on extrahepatic conditions and quality of life, organisations such as the Haemophilia Society, Tainted Blood, The Contaminated Blood Campaign and the Manor House Group were contacted and asked to provide their views via individual, face-to-face meetings. Their views informed decisions about which extrahepatic conditions to focus on during synthesis.

The National Hepatitis C Register was briefly assessed as a potential source of information. This was done in order to understand the prevalence of extrahepatic conditions and the associations with morbidity and mortality in iatrogenically infected persons in the UK. This database was established in 1998 in order to track the natural history of HCV infection in UK patients. It contains anonymised data of, amongst others, patients who acquired HCV by transfusion.

9.2 Searching

Thesaurus-specific and free-text search terms were developed for the concepts of 'hepatitis C', 'extrahepatic conditions' and 'health-related quality of life'. The database search strategy and search terms were developed initially in PubMed and translated to other sources. The PubMed search strategy is presented in Appendix 1. The search combined the concept Hepatitis C with either: extrahepatic conditions,

observational study designs, or quality of life measures. Thesaurus-specific and free-text search terms were developed for each concept. Test searches showed that the concept 'extrahepatic conditions' is inadequately described in research abstracts and database indexing, and to counter this limitation, search terms to capture observational studies were used.

The search was undertaken on a range of international and regional health and social science databases, and supplemented by browsing websites of advocacy groups and searching key websites that contain healthcare research.

Several sources of published studies informed this analysis, including:

1. Websites
   - Hepatitis C Trust
   - Haemophilia Society
   - Macfarlane Trust
   - Contaminated Blood Campaign
   - taintedblood.info
   - British Liver Trust
2. Databases
   - PubMed
   - EMBASE
   - CINAHL
   - PsycInfo
   - Cochrane Database of Systematic Reviews
   - Centre for Reviews and Dissemination databases (DARE, HTA, NHS EED)
   - HMIC
   - Index Medicus for the Eastern Mediterranean Region
   - ASSIA
   - Sociological Abstracts
   - Social Sciences Citation Index
   - LILACs
   - WHOLIS
   - WHO-EVIPNET
3. Focused searches of search engines and web databases
   - Fade: The North West Grey Literature Service http://www.fade.nhs.uk (accessed 30 June 2014)
   - Google Scholar
   - King's Fund
   - NHS Evidence
   - Opengrey
   - Zetoc
4. Reference lists of included studies

   Although the protocol proposed undertaking forward citation searches and hand searching of key journals, the timelines and large volume of located literature meant we were unable to undertake this method of searching.

9.3 Screening and inclusion/exclusion criteria

The screening process

Because of the timelines of the review, text-mining methods were applied to rank all studies found in terms of likelihood for inclusion. This meant that the most potentially relevant studies were screened first, thus reducing the likelihood of missing key studies at a later stage.

There were two types of screening. First, reviewers used reference titles and abstracts to decide whether or not to exclude a study. At the same time as this screening, studies were also given codes to identify them as being focused upon quality of life, extrahepatic conditions or both.

These codes were then used to identify studies for inclusion in a systematic map of the literature for discussion by our Scientific Advisory Group. For this map, studies included at the title and abstract stage of screening by the date of the Group meeting were coded using a brief set of descriptive codes describing the study focus (extrahepatic conditions or quality of life, or both), which extrahepatic conditions were examined, country, sample size and study design. This map was only able to describe part of the literature (approximately half of our references had been screened prior to the Group's meeting), but was useful to indicate the likely prevalence of different kinds of studies in the literature as a whole.

The full reports of studies that had been included using titles and abstracts were retrieved and screened further. Additional inclusion criteria were added to the screening process at this point, so as to identify sub-sets of studies for synthesis.

Criteria for the systematic map of research

In order to be included and described in our systematic map of research, studies needed to:

- be published since 1990 (since blood products were screened nationally for Hepatitis C from 1991); **AND**
- be published in English; **AND**
- be reports of primary research studies (not reviews or case reports); **AND**
- focus on populations with HCV; **AND**
- examine extrahepatic consequences, complications or conditions of chronic HCV infection; **OR** health-related quality of life (HRQOL), which includes measures of physical and mental health (e.g., factors on the EQ-5D scale such as mobility, self-care, ability to perform usual activities or be employed, pain/discomfort, anxiety/depression) or stigma; **AND**
- have fewer than 50% of its population with HCV exhibiting a compromised liver (i.e. having cirrhosis, hepatocellular carcinoma or a liver transplant); **AND**
- not be a study of the outcomes of treatment, or methods for diagnosis; **AND**
- not be a study of biological markers and/or mechanisms of HCV; **AND**
- have a control or comparison group; **AND**
- not be published solely as a conference abstract or poster.

Studies published before 1991 were not included in searching because it was not possible to detect the HCV virus in blood samples until then (Alter et al. 1989, Hepatitis C Trust 2014), making conclusions about the direct influence of this specific virus on extrahepatic conditions difficult.

Criteria for syntheses

To identify studies for synthesis, all studies meeting the above criteria were screened further using additional criteria. These helped to identify those studies with data for synthesis and to separate studies into those applicable to each of the research questions asked in the review's separate syntheses. To be included in any synthesis, studies had to meet all of the criteria listed above **AND**:

- contain synthesisable data (in the form of outcomes, as opposed to variables used in analyses); **AND**
- not be undertaken solely in certain populations (consisting of people on substance-use treatment programmes or prison populations).

Further criteria were then applied to identify studies for each of the review's syntheses.

Quality of life

To be included in the quality of life synthesis, studies had to meet all the criteria listed above **AND**:

- examine the relationship between HCV and quality of life quantitatively, e.g. by association, relative risk or comparison of means; **AND**
- contain quality of life outcomes measured with validated scales (e.g. SF-36); **AND**
- have comparison groups that were judged to be sufficiently similar on at least two major demographic factors that could be confounding variables (e.g. age, gender, SES, route of acquisition), or have attempted to create such groups (to be judged sufficiently similar, a difference needed to be less than 10% - or 10 years of age - or not reach statistical significance); **AND**
- compare **either**:
  - quality of life outcomes between those with HCV and those without HCV or any other known condition (e.g. healthy populations, general populations); **OR**
  - quality of life outcomes between those with HCV and HIV to quality of life outcomes for people with HIV only.

Depression or anxiety

To be included in the depression and anxiety synthesis, studies had to meet all the criteria listed above **AND**:

- examine the relationship between HCV and depression or HCV and anxiety, e.g. by association, relative risk or comparison of means; **AND**
- contain measures of depression or anxiety; **AND**

- compare either
  - Depression or anxiety outcomes in groups with and without HCV; **OR**
  - Depression or anxiety outcomes in groups co-infected with HCV and HIV versus those infected with HIV alone.

Pain

To be included in the syntheses relating to pain outcomes, studies had to meet all the criteria listed above **AND**:

- examine the relationship between HCV status and pain, or a condition associated with significant bodily or somatic pain, e.g. by association, relative risk or comparison of means; **AND**
- use a reliable and valid measure of pain. Studies gauging pain via the use of subscales within generic health survey questionnaires such as the SF-36 were excluded from the pain syntheses; **AND**
- compare either
  - pain outcomes in groups with and without HCV; **OR**
  - pain outcomes in groups co-infected with HCV and HIV versus those infected with HIV alone.

9.4 Data extraction and quality assessment

Studies included in our syntheses were data extracted (or 'coded') according to study characteristics. These included country of origin and PROGRESS-Plus participant characteristics (e.g. age, gender, socio-economic status, marital status) (Evans and Brown 2003, Kavanagh et al. 2008). They also included study-specific codes, such as the health risk characteristics of the population (e.g. haemophilia, needle sharing, concurrent HBV or HIV infection), type of extrahepatic condition (e.g. glomerulonephropathy, Sicca syndrome) and type of health-related quality of life measure.

All included studies were assessed for quality using previously developed criteria specific to observational studies (Sutcliffe et al. 2011, von Elm et al. 2007). Two reviewers independently rated each study's quality, then met to discuss and agree overall findings (with disagreements resolved by a third reviewer where needed). Studies were assessed for quality across six domains:

1. The appropriateness of comparison groups
2. The extent to which confounders were considered in the analysis
3. Representativeness of the sample to the study's population of interest
4. A reliable measure of HCV
5. A reliable measure of quality of life or extrahepatic condition
6. The appropriate relevance and generalisability of the study to our review's population of interest.

Studies answering 'Yes' to all six criteria were considered to be at 'low' risk of methodological bias; studies answering 'Yes' to either question 1 or 2 and to at least

four questions overall were considered to be at 'moderate' risk of bias; and studies answering 'No' to both questions 1 and 2 were considered at 'high' risk of bias.

9.5 Synthesis

Outcome data were extracted from studies in the form of means and standard deviations, or frequencies, and were used appropriately to calculate effect sizes. Conversions to standardised measures were undertaken where necessary. Meta-analyses were undertaken to examine the relationships between:

1. HCV exposure and health-related quality of life
2. HCV exposure and depression/anxiety
3. HCV exposure and pain.

In general, results were pooled across studies using a DerSimonian-Laird random effects meta-analysis model (Hedges and Vevea 1998). Heterogeneity was assessed using Higgins' I^2 (Higgins et al. 2003). To investigate possible causes of heterogeneity, where there were sufficient studies in a meta-analysis, meta-regressions were performed to examine the influence of factors including: average age, gender distribution and proportion of PWID (Thompson and Sharp, 1999). Potential for publication bias or selective reporting was assessed using funnel plots and Egger's test (Egger et al. 1997).

Quality of life

Separate meta-analyses were conducted for studies with and without HIV co-infection. Meta-analyses were performed for SF36 PCS, MCS and each of the eight SF36 components. The mean quality of life score and its standard deviation in both HCV and control groups were used to calculate the mean difference in quality of life score between HCV and control groups for each SF36 component in each study, along with its standard error. The mean differences between HCV and control groups were pooled across studies.

Depression and anxiety

For the continuous outcomes where depression or anxiety were reported on a scale (e.g. HADS) the mean score and its standard deviation in both HCV and control groups were used to calculate the mean difference in score between HCV and control groups, along with its standard error. As different studies used different measurement scales, the mean differences were converted into standardised mean differences to allow different measurement scales to be pooled in the meta-analyses. The majority of studies reported results using the HADS scale, so the mean differences on the HADS scale were also pooled in a random-effects meta-analysis.

For dichotomous outcomes, where results on prevalence of depression or anxiety were presented, the odds ratio for the comparison between HCV and control groups and its 95% confidence interval were extracted from reports. In these analyses, any degree of depression (mild, moderate, severe) was considered to be a case of depression. Odds ratios adjusted for potential confounding factors were used where

available; if unavailable, unadjusted odds ratios were calculated from the numbers of events reported.

Pain

Separate meta-analyses were conducted for arthralgia (including joint pain) and fibromyalgia. Numbers of people with arthralgia and fibromyalgia were extracted from groups with and without HCV in order to calculate the relative risk of having the outcome with HCV, with its 95% confidence interval.

The results of quality appraisal were not used to determine whether or not studies should be entered into statistical meta-analyses. Meta-analyses therefore contained studies judged to be at risk of bias. Although *at risk* of bias, the studies were not *necessarily* fundamentally flawed, particularly where quality appraisal may have been affected by insufficient reporting rather than inappropriate study design.

However, the findings of studies judged to be of high or moderate risk of bias were considered suspect and potentially misleading. Where effect sizes from these studies could not be incorporated into a meta-analysis (in order to compare consistency and magnitude of effect within a body of similar studies), we did not report their findings in any narrative synthesis.

9.6 Quality assurance

All searches, screening results, codes and syntheses were housed in and conducted with specialist research software, EPPI-Reviewer (Thomas et al. 2010). EPPI-Centre information scientists, using background literature cited in the protocol, identified free-text search terms (e.g. 'extrahepatic', 'extra-hepatic'). These were developed and combined with thesaurus-specific terms held within MEDLINE, and translated into each subsequent electronic source (Gough et al. 2012). A second researcher checked search terms to ensure accuracy.

Using an electronic inclusion/exclusion tool containing definitions, two researchers independently screened a subset of references, and then met to compare and agree ratings. A third member of the research team resolved disagreements on inclusion. When a sufficient level of inter-rater reliability was reached (e.g. 80% or higher), the remaining studies were screened by a single researcher only. Three quality checks were undertaken on a random sample of screened studies during the process, and results fed back to individual screeners to inform their screening.

Coding for the map was conducted by individual researchers, using code sets developed for the review. Coding and quality assessment of the studies included in the syntheses was conducted by two researchers working independently, who then met to agree and resolve disagreements. A third member of the research team resolved disagreements when this was needed.

To ensure the quality of outcome extraction and synthesis, two researchers independently extracted data for synthesis and met to agree findings (with discrepancies resolved by a third). The researchers used outcome extraction tools developed and tested for standard extraction. One reviewer conducted the syntheses

with appropriate statistical and methodological guidance from other team members, using appropriate specialist software.

9.7 Grading the strength of evidence

Overall strength of the conclusions was based on two considerations: the consistency and sufficiency of the evidence base.

Consistency refers to whether or not studies agreed about the direction of findings (GRADE Working Group 2004):

- A completely consistent evidence base would have 100% of included studies in agreement about the direction of findings (e.g. an increased likelihood of suffering from a particular extrahepatic condition).
- A moderately consistent evidence base would have 75-99% of studies agreeing about the direction of findings.
- An inconsistent evidence base would have fewer than 75% of studies agreeing on the direction of findings.

Sufficiency refers to whether the quality and the quantity of the available evidence are adequate for drawing overall conclusions (i.e. a minimum number of studies without a high risk of bias). Here we have stipulated that at least four studies without a high risk of bias must be present to draw strong conclusions.

The strength of the evidence for each conclusion was graded drawing on assessments for consistency and sufficiency; Table 9.1 provides details of the grading system.

Table 9.1: Grading system for the strength of evidence: consistency and sufficiency

Grade	Criteria	Rationale
Strong	At least four studies with low or moderate risk of bias whose findings meet the criterion for consistency (i.e. 75-100% agree about the direction of findings).	• Evidence corroborated by a large number of reliable studies. • The pattern indicates that additional high-quality evidence would be very unlikely to contradict the overall conclusions. • Even if an additional study with contradictory evidence were found, the overall consistency of the evidence base would probably remain above 75%.
Promising	Two or three studies with low or moderate risk of bias whose findings meet the criterion for consistency (i.e. 75-100% agree about the direction of findings).	• Reliable evidence corroborated by at least one other study. • Patterns indicate that additional high-quality evidence would be unlikely to contradict the overall findings. • If an additional high-quality study with contradictory evidence were found, the overall consistency of the evidence base would probably fall below 75%.

Grade	Criteria	Rationale
Tentative	Single study with low or moderate risk of bias.	• The findings are reliable but uncorroborated. • No patterns in the evidence can be determined. • Identification of a high-quality study with contradictory evidence would change our overall conclusions.
Inconclusive	Evidence only available from studies with a high risk of bias.	• The findings are neither reliable nor corroborated. • No overall conclusions can be drawn.

10. Flow of studies through the review

This chapter describes the process of identification of the 71 included studies from within the pool of over 50,000 studies identified by our systematic searches. It provides:

- a narrative account of the flow of studies through the review
- a graphic representation of the flow of studies through the review

10.1 Studies identified by searches

The review's extensive searching identified a total of 55,989 potentially relevant references. A total of 55,151 came from database searches. A further 838 references were identified from website searches (n=603) and reference list searching (n=235).

10.2 Accounting for the studies seen during the review

The entire process of screening references is illustrated in Figure 10.1. The separate stages of screening are described below in turn. The systematic map was produced approximately half way through screening all studies on title and abstract and was not updated after it had served the function of informing our consultation discussions. In addition, the coding for each study was done only by a single reviewer. It is important to note that due to these factors the findings of the map are likely to be imprecise. First, studies will have been identified after this, which, if coded, would act to change the numbers of different kinds of EHC represented in the map. Second, because the coding was by a single reviewer, it is also likely to contain inaccuracies. Nonetheless, the description in Chapter 11 gives an indication of the likely proportions of different kinds of EHC in the literature as a whole.

Screening studies for inclusion

A total of 36,141 studies were excluded by screening reference titles and abstracts. The reasons for exclusion are summarised in Table 10.1.

Table 10.1: Screening on abstract

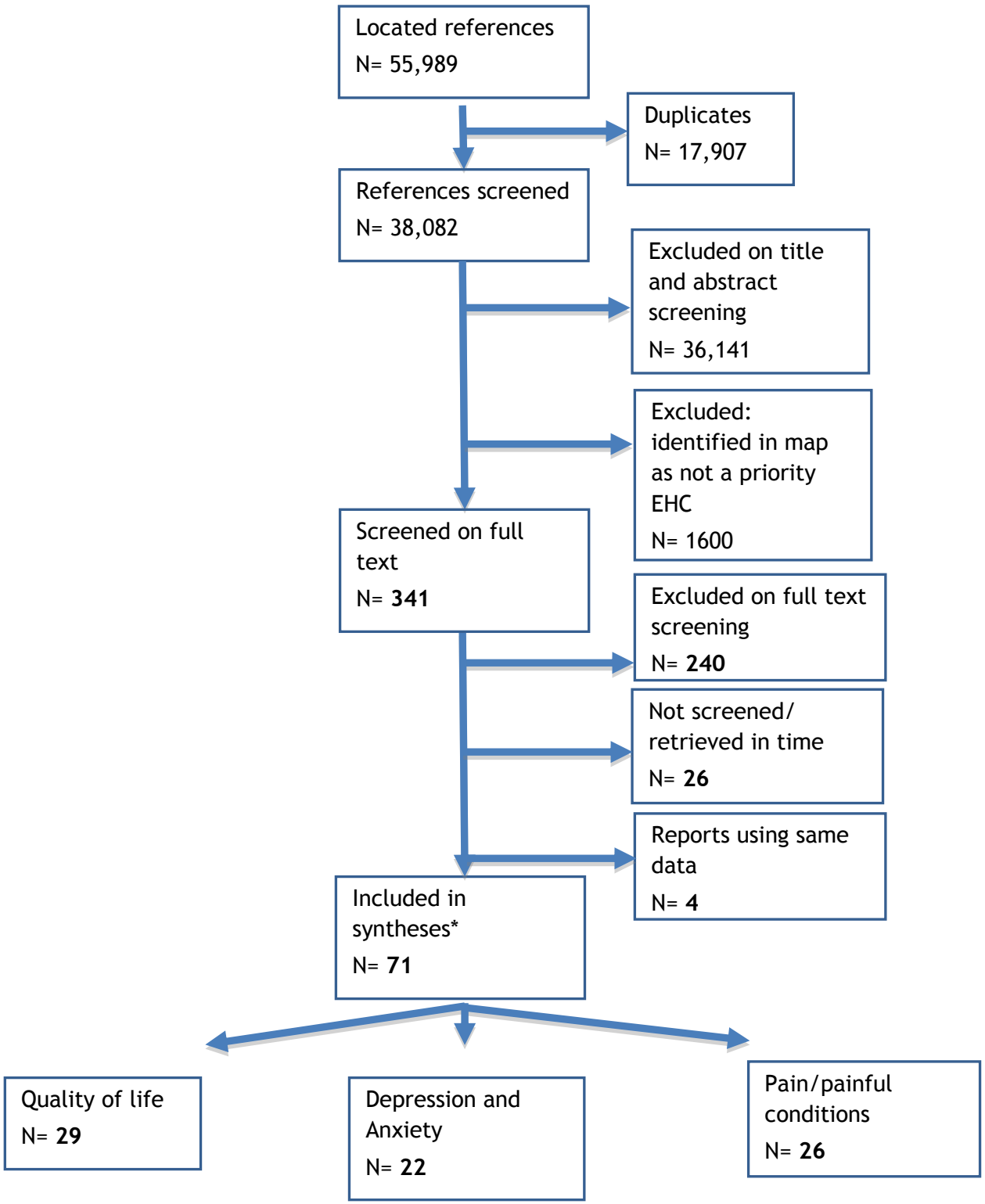
Number	Exclusion criteria	Number of excluded studies
EXC 1	Not 1991 onward	139
EXC 2	Not in English language	1,542
EXC 3	Not primary research or are case reports	7,554
EXC 5	Not about hepatitis C	3,720

Number	Exclusion criteria	Number of excluded studies
EXC 6	Not quality of life (HRQOL) or extrahepatic condition (EHC)	17,771
EXC 8	Compromised liver patients	1,568
EXC 9	Treatment or diagnostic tests of HCV or EHC	2,762
EXC 10	Biological markers/mechanisms of EHC	861
EXC 11	No control or comparison group	116
EXC 12	Conference abstract or poster	108
	Total excluded	36,141

Most references were excluded because they did not focus on either quality of life or extrahepatic conditions (17,771). A total of 7,554 references were excluded at this point because they did not describe primary research (e.g. they were editorials, guidelines, or reports of single medical cases).

Figure 10.1: Flow of studies through the review

* Several studies occurred in more than one synthesis



After the identification of priority extrahepatic conditions (depression and anxiety, pain) all studies in the map that were identified as not being focused on one or more of these conditions were set aside and examined no further. A total of 1,600 studies were excluded at this point. Full-text reports were sought for the remaining studies, as well as for those new studies identified as focused on quality of life and/or the priority EHC areas.

A second round of screening was undertaken on the full reports of 341 references. The criteria applied at this point, with the number of studies excluded under each criterion, are illustrated in Table 10.2.

Table 10.2: Screening of full report

Exclusion criteria	**Number of excluded studies**
Not in English language	10
Not primary research/case reports	5
Not about chronic hepatitis C	1
Not HRQOL or EHC	12
Compromised liver patients	2
Treatment or diagnostic tests of HCV or EHC	12
Biological markers/mechanisms of EHC	5
No control or comparison group	49
Conference abstract or poster	43
No synthesisable data	28
Non-relevant population	20
Not answering synthesis questions	52
HRQOL general population insufficient matching	25
Not screened or retrieved in time	26
Linked reports that use same data	4
Total number of studies with one or more exclusion code	270

* Numbers do not add up to 270 as several studies had multiple analyses that were given different codes

At this stage, the most frequent reason for excluding a study was that it did not address the specific questions being asked by the syntheses (n=52). Studies examining the association between HCV and quality of life, for example, were excluded if a comparison was made, not with a healthy or general population sample, but with people who had hepatitis B, or between chronic HCV of different levels of severity. Other common reasons for exclusion at this stage were that the studies had not used a comparison group for the analysis of interest (n=49) or were presented only in conference abstracts or posters (n=43).

The studies included in the final syntheses

This left a total of 71 studies included in the final syntheses: 29 studies of quality of life in people with HCV compared with healthy or normal populations, 22 studies examining the association between HCV and depression or anxiety, and 26 studies of the association between HCV and pain. Some of these studies examined more than one association. Four examined associations between HCV and both quality of life and depression or anxiety (Ashrafi et al. 2012, Cordoba et al. 2003, Heeren et al. 2013, Lowry et al. 2010) and one studied the association of HCV with depression, anxiety and pain (Goulding et al. 2001).

10.3 Identifying priority areas for synthesis

As summarised in Section 3.3, we sought information from three sources, and briefly examined the National Hepatitis C Register, so as to determine which extrahepatic conditions should be prioritised for this review:

- Our Scientific Advisory Group (to determine which conditions had the highest morbidity/mortality and were not yet synthesised)
- Members of four patient advocacy groups (to determine which conditions had a significant impact on people's quality of life)
- The evidence base of located literature (to determine which topics had the most research and were not yet synthesised).

The information provided by each source is laid out in turn below.

Consultation with Scientific Advisory Group

We met with our Scientific Advisory Group in mid-February 2014, and presented a draft of the systematic map of the literature. We asked for guidance on issues to address in our analyses and for perspectives on which extrahepatic conditions merited particular investigation.

Advisory Group members noted the challenges of controlling for multiple confounders, the risks involved in combining findings when studies utilise different comparison groups, the advantages and disadvantages of using small cross-sectional studies versus nationally representative samples, and the need to work from the best available evidence, which would vary from topic to topic.

The group discussed some extrahepatic conditions, including cryoglobulinaemia, non-Hodgkins lymphoma, insulin resistance and diabetes. However, they did not prioritise a set of extrahepatic conditions on which to focus. Group members

suggested that extrahepatic conditions with the highest morbidity and mortality should be prioritised, but the group recognised that patient perspectives on morbidity and mortality might differ from those published in the medical literature.

Consultation with advocacy groups

We consulted in February and March 2014 with members of four organisations: The Hepatitis C Trust, The Haemophilia Society, Tainted Blood and Contaminated Blood. Consultations were attended by between one and three representatives of each organisation. Sessions lasted between 1.5 and 4 hours, and were tape recorded, with informed consent obtained from members at the beginning of each consultation. A total of three women and four men were consulted.

The identification by advocacy groups of those EHCs most affecting quality of life

Advocacy group representatives identified a total of eighteen extrahepatic conditions that impacted significantly on quality of life. These are illustrated in Table 10.3.

Table 10.3: Priority extrahepatic conditions identified by advocacy groups (n=18)

Condition	**Advocacy groups identifying this EHC**	**Research on this topic identified in the map**
Depression/anxiety	4	148/42
Pain	4	31
Fatigue	4	66
Cognitive function (including insomnia)	3	113
Brittle teeth	2	2 (Dental) 23 (bone mineral density/ osteoporosis)
Cardiovascular disease/circulation problems	2	163
Headaches (tension headache)	2	3
Thyroid problems	2	55
Bladder problems	1	0
Breast cancer	1	4

Condition	Advocacy groups identifying this EHC	Research on this topic identified in the map
Cerebral haemorrhage	1	7
Diabetes mellitus	1	244
Gallstone disease	1	12
Irritable bowel disease	1	5
Lung disease	1	22
Prostate problems	1	1
Renal problems	1	145
Vitamin D deficiency	1	6

As this table shows, all four groups identified depression and anxiety, pain and fatigue as significant extrahepatic conditions. Impaired cognition (e.g. 'brain fog', short-term memory loss, insomnia) was identified by three of the four advocacy groups.

Advocacy group descriptions of EHCs and quality of life

Living with symptoms or conditions such as those noted above were described as limiting people's physical functioning. Advocacy group members noted that depression and anxiety, pain, fatigue and cognitive function most often prevented them from undertaking normal daily activities. As an illustration, four out of the seven attendees later mentioned that the act of attending meetings with us in central London meant that they were exhausted for two to three days following. The unpredictability and severity of symptoms (and pain in particular) meant that people living with HCV could not always plan to attend events in advance.

Advocacy group members also spoke of the impact of other people's attitudes about their HCV, describing feeling stigmatised. They cited job losses and harassment, and loss of friendship due to fears of infection, as some of the negative social impacts of the disease, brought out into the open because of the limitations caused by some of the conditions listed above, in addition to the condition itself. Three of the four groups noted that people living with HCV were more stigmatised by their peers and by health care professionals, in comparison to those infected with HIV alone. Diagnosis and treatment were also described as impacting on personal relationships, with partners also experiencing the stresses of living with HCV.

The impact of extrahepatic conditions on quality of life was described as circular: pain, fatigue, depression or anxiety led to uncertainty about health, social and

financial issues, which in turn led to greater depression or anxiety. For example, some people with HCV were not able to work because of depression. However, trying to do something about these problems could involve lengthy dealings with bureaucracy in order to get health, social or financial assistance to cope, and this could further add to the condition's severity.

Some things helped people to manage the conditions they associated with their HCV infection. Meditation was found to be useful for some people experiencing painful conditions. Advocacy groups noted that rapid, priority access to the right treatment helped them to manage more effectively. In particular, there was some consensus that brief counselling sessions (i.e. six to eight weeks) for dealing with what was often a set of long-term conditions was not enough. They also described situations where treatment would have been better had it been provided by professionals with expertise in both HCV and the specific extrahepatic condition. Those consulted did not note any particular patterns in specific extrahepatic conditions being experienced by particular groups.

Finally, advocacy group members noted a need for research to be undertaken on:

- how the experience of diagnosis impacts on the ways in which people cope with HCV treatment and disease progression
- the impact of HCV diagnosis and treatments on people's relationships with partners and spouses
- the long-term family, health and social impacts of HCV treatment on patients
- the impact of ageing on quality of life in haemophiliacs with HCV
- the long-term health issues in HCV patients who have spontaneously cleared the HCV virus
- patients' and professionals' views of the differences in stigmatisation between those people co-infected with HCV and HIV, compared to those with HIV alone.

The National Hepatitis C Register

This source was identified late in the review process and its information could not be fully integrated within the timeframe of this project. A brief examination, however, did identify that some of the questions asked of Register participants potentially refer to extrahepatic conditions. Therefore, this register is likely to be a key source for understanding significant morbidity and mortality in iatrogenically infected patients living with HCV. Retrieval and analysis of data from the Register and the need for both data linkage and location and assembly of an appropriate comparison group would require adequate time for the careful design and implementation of a robust research study in order to obtain a reliable answer.

10.4 Deciding on the areas for synthesis

As described above, all four advocacy groups identified depression and anxiety, pain and fatigue as significant extrahepatic conditions impacting on quality of life, and cognitive function was identified by three of the four groups. In order to keep to our allotted timeline and resource, we were unable to examine the

relationships between HCV and all of these conditions. Instead, we focused on the first three for synthesis.

11. Descriptive map of extrahepatic conditions

Evidence from the located literature identified a wide range of extrahepatic conditions, involving all body systems. Many of these conditions were not identified by the advocacy group representatives as being significant. The following tables summarise extrahepatic conditions identified by systemic involvement.

It must be noted that the numbers of papers do not add up to the total number of identified papers (n=1,776) screened and coded for this map, or the number of research reports studying the extrahepatic condition by systemic involvement. This is because papers often discussed more than one extrahepatic condition in relation to HCV. Conditions that were identified by the advocacy group members are marked with an asterisk and are shown in Tables 11.1 to 11.16. In addition, the mapping process described in Chapter 9 identified a total of 92 studies that had in some way examined the association between HCV and quality of life. Since these studies are not concerned with extrahepatic conditions, they are not described further here.

In general, the most commonly studied associated extrahepatic condition was diabetes mellitus (n=244), which was identified by one advocacy group. The next six most commonly researched extrahepatic conditions were non-Hodgkin's lymphoma (n=162), mixed cryoglobulinaemia (n=159), depression (n=148), cognitive dysfunction (n=113), insulin resistance (n=106) and lichen planus (n=98). Depression and cognitive dysfunction were clearly identified by all of the advocacy groups, and mixed cryoglobulinaemia is encompassed within circulation problems that were also identified. Non-Hodgkin's lymphoma and lichen planus emerged as important extrahepatic conditions, with significant numbers of studies being identified. It must be noted that the extrahepatic conditions have been organised according to body system involvement and there is a degree of overlap for some conditions, which could appear under more than one system heading.

11.1 Neurological conditions

Neurological conditions had the highest number of reported studies (n=438) and the majority of advocacy groups identified four of the five identified neurological conditions as being important; depression (n=148), cognitive dysfunction (n=113), fatigue (n=66) and anxiety (n=42). Peripheral or central neuropathies also had a significant number of studies (n=43) but this was not identified by the advocacy groups.

Table 11.1: Neurological extrahepatic conditions by number of research reports (n=438)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Neurological conditions		*438*
1	Depression*	148
2	Cognitive dysfunction*	113
3	Fatigue*	66
4	Peripheral/central neuropathies	43
5	Anxiety*	42
6	Mental illness (general/unspecified)	26

* Identified by advocacy group

11.2 Metabolic disorders

The second largest number of studies focused on metabolic disorders. The advocacy groups identified the most commonly reported condition, diabetes mellitus (n=244). The search returned a significant number of studies that focused on pre-diabetic conditions: insulin resistance (n=106) and metabolic syndrome (n=25). Disruptions in cholesterol and lipid production were also studied (n=17).

Table 11.2: Metabolic extrahepatic conditions by number of research reports (n=339)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Metabolic disorders		*339*
1	Diabetes mellitus*	244
	a) Type 2	87
	b) Post transplant diabetes mellitus (PTDM)	24
	c) Type 1	8
	d) Gestational	1
2	Insulin resistance	106
3	Metabolic syndrome	25
4	Hypercholesterolaemia/hyperlipidaemia	17

Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
5 Iron overload	3
Unspecified metabolic involvement	*1*

* Identified by advocacy group

11.3 Lymphoproliferative disorders

The third highest number of studies (n=269) were returned for lymphoproliferative extrahepatic conditions. Eleven distinct conditions were identified. Non-Hodgkin's lymphoma was the most commonly studied (n= 162) and where sub-group was specified, marginal zone lymphoma returned the highest number of studies (n=15).

Table 11.3: Lymphoproliferative extrahepatic conditions by number of research reports (n=269)

Systemic involvement and extrahepatic condition	**Number of research reports studying this EHC**
Specific lymphoproliferative conditions	*269*
1. Non-Hodgkin's lymphoma	162
a) Marginal zone lymphoma (MZL)	15
b) Diffuse large B-cell lymphoma (DLBCL or DLBL)	12
c) Mucosa-associated lymphoid tissue lymphoma (MALT)	10
d) Waldenstrom's lymphoma	9
e) Burkitt's lymphoma	3
f) Salivary gland MALT lymphoma (SGML)	1
g) Lymphoblastic lymphoma	1
2 Mixed cryoglobulinaemia*	159
3 Hodgkin's lymphoma	27
4 Chronic lymphocytic leukaemia	13
5 Multiple myeloma	9
6 Lymphadenopathy	6
= Acute lymphoblastic leukaemia	6
8 Acute myeloid leukaemia	5
9 Chronic myeloid leukaemia	2
10 Hairy cell leukaemia	1
= HIV related lymphoma	1
Unspecified lymphoproliferative condition	*2*

* Identified by advocacy group

11.4 Integumentary conditions

Thirty specific integumentary or skin-related extrahepatic conditions were studied, making this the system with the widest variety of extrahepatic studies, the most

common being lichen planus (n=98), porphyria cutanea tarda (n=33) and psoriasis (n=22). Advocacy groups did not identify skin conditions as a priority in this instance.

Table 11.4: Integumentary/skin-related extrahepatic conditions by number of research reports (n=202)

	Systemic involvement and extrahepatic condition	**Number of research reports studying this EHC**
Specific integumentary/skin conditions		*202*
1	Lichen planus	98
2	Porphyria cutanea tarda	33
3	Psoriasis	22
4	Erythema	17
5	Pruritis	13
6	Urticaria	9
7	Vitiligo/hyperpigmentation/hypopigmentation	6
8	Xerostomia	4
9	Alopecia areata	3
=	Photosensitivity	3
=	Angioedema	3
12	Xerophthalmia	2
=	Nailfold abnormalities (proximal)	2
=	Myosis fungoides lesions	2
15	Skin rashes (general)	1
=	Cellulitis	1
=	Rosacea	1
=	Seborrhoeic dermatitis	1
=	Spider naevi	1
=	Telangiectasia	1

Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
= Varicose veins	1
= Pigmented pupuric dermatosis	1
= Gingivitis	1
= Adipose tissue alterations	1
= Oral lesions	1
= Keratitis	1
= Prurigo	1
= Sarcoidosis	1
= Necrotising fasciitis	1
= Ecchymosis	1
Unspecified integumentary conditions	*3*

11.5 Cardiovascular/circulatory conditions

Cardiovascular and circulatory problems in general were identified as a priority by two advocacy groups. Our review identified 14 specific conditions, with the most commonly studied being hypertension (n=63). Second was vasculitis (n=62), an umbrella term for inflammatory blood vessel disorders that incorporates a number of varieties and manifestations; due to the scope of the review, these have been grouped together. Atherosclerosis (n=22) was the third most common cardiovascular extrahepatic condition studied, followed by myocardial infarction and cardiomyopathy, both with 13 studies.

Table 11.5: Cardiovascular extrahepatic conditions by number of research reports (n=163)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
*Cardiovascular disorders**		*163*
1	Hypertension	63
2	Vasculitis	62
3	Atherosclerosis	22
4	Myocardial infarction	13
=	Cardiomyopathy	13
6	Myocarditis/myofibrosis	6
=	Ischaemic heart failure	6
8	Raynaud's' syndrome	2
=	Congestive heart failure	2
=	Arrhythmias	2
11	Pulmonary embolism	1
=	Deep vein thrombosis	1
=	Unstable angina	1
=	Chest pain	1
Unspecified cardiovascular involvement		*59*

* Identified by advocacy group

11.6 Renal conditions

Seven renal extrahepatic conditions were studied, with membranoproliferative glomerulonephritis producing the most studies (n=63), followed by chronic kidney disease (n=26). Only one advocacy group identified renal problems as a priority. One advocacy group identified bladder problems as a priority; the closest study returned was for unspecified urinary abnormalities (n=1).

Table 11.6: Renal extrahepatic conditions by number of research reports (n=145)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
*Renal conditions**		*145*
1	Membranoproliferative glomerulonephritis	63
2	Chronic kidney disease (CKD)	26
3	Nephrotic syndrome/nephropathy	8
4	End stage renal disease	5
5	Urethritis	1
6	Nephrolithiasis	1
7	Urinary abnormalities*	1
Unspecified glomerular disease		*6*

* Identified by advocacy group

11.7 Haematological conditions

Ten haematological conditions were studied, with thrombocytopenia producing the most studies (n=48), followed by anaemia (n=31). No haematological conditions were identified by the advocacy groups; however, mixed cryoglobulinaemia was identified as a priority condition, and is classified as both a haematological and a lymphoproliferative condition. For this review, it is included under lymphoproliferative conditions.

Table 11.7: Haematological extrahepatic conditions by number of research reports (n=116)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Haematological conditions		*116*
1	Thrombocytopenia	48
2	Anaemia	31
3	Monoclonal gammopathy	8
4	Thalassaemias	7
5	Neutropaenia	4
6	Thromboembolism	2

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
7	Agranulocytosis	1
=	Leukopenia	1
=	Haemochromatosis	1

11.8 Musculoskeletal conditions

Musculoskeletal extrahepatic involvement produced 108 papers, studying 7 conditions. A further extrahepatic manifestation studied was joint arthroplasty (n=1), but this is not an extrahepatic condition, rather a corrective surgical procedure to alleviate joint pain and improve joint articulation. Pain was identified by all four advocacy groups; this was combined with arthralgia and fibromyalgia syndrome (n=31). Brittle teeth were identified by two advocacy groups but the review did not identify studies specifically focused on this. Related conditions did surface as significant, those being bone mineral density/osteoporosis and papers focused on dental manifestations (n=3). The abstracts for these were somewhat unclear as to the nature of the dental condition, which were described as dental disease or dental pulp disorders (n=2) and oral disease (n=1).

Table 11.8: Musculoskeletal extrahepatic conditions by number of research reports (n=108)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Musculoskeletal conditions		*108*
1	Rheumatological disease	32
2	Pain/arthralgia/FS*	31
3	Bone mineral density/osteoporosis*	23
4	Rheumatoid arthritis	17
5	Carpal tunnel syndrome	2
6	Ankylosing spondylitis	1
6	Necrotising myositis	1
Unspecified musculoskeletal conditions		*1*

* Identified by advocacy group

11.9 Autoimmune/immunodeficiency conditions

Autoimmune or immunodeficiency extrahepatic involvement produced 103 papers, focusing on four conditions. None of these conditions were highlighted by the advocacy groups. Sicca syndrome (n=34) and systemic lupus erythematosus (n=34) were the joint most commonly reported autoimmune extrahepatic conditions.

Table 11.9: Autoimmune/immunodeficiency extrahepatic conditions by number of research reports (n=103)

	Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
Autoimmune/immunodeficiency conditions		*103*
1	Sicca syndrome	34
=	Systemic lupus erythematosus	34
3	Antiphospholipid antibody syndrome (APS)	19
4	Myasthenia gravis	1

11.10 Gastrointestinal conditions

Gastrointestinal extrahepatic involvement produced 81 papers, studying 19 conditions. The most commonly studied conditions were unspecified gall bladder and bile duct disorders (n=29); this was followed by gallstones (n=12), which was identified as important by one advocacy group. Vitamin D deficiency (n=6) and irritable bowel disease (n=5) were also identified by a single advocacy group and were ranked 6th and 7th in the number of gastrointestinal extrahepatic condition studies.

Table 11.10: Gastrointestinal extrahepatic conditions by number of research reports (n=81)

	Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
Gastrointestinal conditions		*81*
1	Gall bladder/bile duct disorders	29
2	Gallstones*	12
3	Vitamin deficiencies (general)	9
4	Coeliac disorder	7
=	Pancreatitis	7

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
6	Vitamin D deficiency*	6
7	Irritable bowel disease (IBD)*	5
8	Malnutrition	2
=	Peptic ulcer disease	2
=	Oesophageal variceal bleeding	2
=	Salivary flow	2
=	Weight loss	2
=	Diarrhoea	2
=	Nausea	2
15	Poor appetite	1
=	Food intolerance	1
=	Ischaemic colitis	1
=	Obesity	1
=	Gastritis	1
Unspecified gastrointestinal involvement		*1*

* Identified by advocacy group

11.11 Cancers

There were 20 specific types of cancer identified in this review, yielding 73 papers. A further eight papers discussed cancer but did not specify the organ or system involved. The highest number of studies were for pancreatic cancer (n=6). Breast cancer was identified by one advocacy group as significant and was the second most commonly studied extrahepatic cancer (n=4), jointly with colorectal cancer (n=4), followed by lung cancer (n=3) and squamous cell carcinoma (n=3). Prostate problems were identified by one advocacy group, and although no specific prostate studies were captured in general reproductive studies, one study on prostate cancer was found.

Table 11.11: Extrahepatic cancer by number of research reports (n=70)

	Systemic involvement and extrahepatic condition	**Number of research reports studying this EHC**
Extrahepatic cancer		*73*
1	Pancreatic	6
2	Colorectal	4
=	Breast*	4
4	Lung	3
=	Squamous cell carcinoma	3
6	Kaposi's sarcoma	2
=	Stomach	2
8	Anal	1
=	Renal	1
=	Meningioma	1
=	Glioblastoma	1
=	Oesophageal	1
=	Cervical	1
=	Vulva	1
=	Ovarian	1
=	Lingual	1
=	Testicular	1
=	Prostate*	1

* Identified by advocacy group

11.12 Endocrine conditions

The endocrine system was studied in relation to HCV in 70 studies. The majority of papers focused on a range of thyroid conditions (n=55), which were identified as important by two Advocacy groups. The nature of endocrine dysfunction was unclear in eight papers but, of the remaining specified endocrine conditions, only hypogonadism (n=2) had more than one study.

Table 11.12: Endocrine extrahepatic conditions by number of research reports (n=70)

System involvement and extrahepatic condition		Number of research reports studying this EHC
Endocrine dysfunction conditions		*70*
1	Thyroid conditions*	55
	a) Thyroiditis	18
	b) Hypothyroidism	17
	c) Hyperthyroidism	4
2	Hypogonadism	2
3	Hyperparathyroidism	1
=	Growth disorder	1
=	Thymic dysfunction	1
=	Hypoparathyroidism	1
=	Pseudoaldosteronism	1

* Identified by advocacy group

11.13 Cerebrovascular conditions

There was an even distribution of studies relating to ischaemic and haemorrhagic strokes (n=7). Two advocacy groups identified tension headaches (n=3), and one identified cerebrovascular haemorrhage as important. However strokes, ischaemic (n=7), haemorrhagic (n=7) and unspecified (n=5), were the most commonly studied extrahepatic cerebrovascular condition.

Table 11.13: Cerebrovascular extrahepatic conditions by number of research reports (n=27)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Cerebrovascular disease		*27*
1	Ischaemic stroke	7
=	Haemorrhagic stroke/cerebrovascular event*	7
3	Stroke unspecified	5

Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
4 Tension headache*	3
5 Trans-ischaemic attack	1

* Identified by advocacy group

11.14 Pulmonary conditions

Lung disease was highlighted by one advocacy group. Seven specific conditions were identified; the most studies were reported for chronic obstructive pulmonary disease (n=9), followed by pulmonary fibrosis (n=5) and interstitial pulmonary disease (n=3).

Table 11.14: Pulmonary conditions by number of research reports (n=22)

Systemic involvement and extrahepatic condition	Number of research reports studying this EHC
*Pulmonary/lung disease**	*22*
1 Chronic obstructive pulmonary disease (COPD)	9
2 Pulmonary fibrosis	5
3 Interstitial pulmonary affection/disease	3
4 Asthma	2
5 Emphysema	1
= Pulmonary haemorrhage	1
= Mycoplasma pneumoniae	1

* Identified by advocacy group

11.15 Reproductive conditions

The most commonly studied of the six reproductive extrahepatic conditions was sexual and erectile dysfunction (n=7). Six studies looked at the impact of semen or sperm changes and only single studies for the remaining four conditions were identified.

Table 11.15: Reproductive extrahepatic conditions by number of research reports (n=17)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Reproductive system disorders		*17*
1	Sexual/erectile dysfunction	7
2	Semen or sperm changes	6
3	Menopausal status/symptom	1
=	Impaired ovarian function	1
=	Gynecomastia	1
=	Testosterone deficiency syndrome	1

* Identified by advocacy group

11.16 Special senses conditions

The number of extrahepatic conditions studied that involved the ears or eyes directly was low (n=3), reflected in the number of studies conducted (n=7).

Table 11.16: Special sense extrahepatic conditions by number of research reports (n=7)

Systemic involvement and extrahepatic condition		Number of research reports studying this EHC
Special sense disorders		*7*
1	Cataract	1
2	Raised intraocular pressure	1
3	Blepharitis	1
Unspecified hearing		1
General ocular involvement		4

11.17 Other extrahepatic conditions

There were a number of other non-specific extrahepatic conditions studied (n=8). These were mainly infective disorders, e.g. tuberculosis (n=4), Rift Valley fever (n=1), leprosy (n=1), or non-specific manifestations, e.g. AIDS-related conditions (n=2), flu-like symptoms (n=1) or autonomic dysfunction (n=1).

There were a significant number of studies (n=120) that focused on the impact of hepatitis on transplant or partial allograft outcomes. The majority of these studies were on renal transplants/allografts (n=103), followed by heart (n=7), lung (n=3), pancreas (n=3) and bone marrow/haemopoietic transplants (n=3).

Appendices

Appendix 1: Search strategy

PubMed

Date searched: 9 December 2013

No. of records: 19,195

Search	Query	Items found
#25	#22 OR #24	19195
#24	Search (#14 NOT #23)	18057
#22	Search (#21 NOT #15)	2199
#21	Search (#20) AND ("2005"[Date - Publication] : "3000"[Date - Publication])	2204
#20	Search (#19 AND #1)	3201
#19	Search (#17 OR #18)	618228
#18	Search (HRQL[tiab] OR DALY[tiab] OR HRQOL[tiab] OR "Health state"[tiab] OR "Health status"[tiab] OR "Health year"[tiab] OR "Health years"[tiab] OR "Healthy years"[tiab] OR "Healthy year"[tiab] OR HYE[tiab] OR HYEs[tiab] OR "Quality adjusted life"[tiab] OR "Quality of life"[tiab] OR QOL[tiab] OR "Life quality"[tiab] OR Qaly[tiab] OR Utility[tiab] OR utilities[tiab] OR Wellbeing[tiab] OR "Well being"[tiab] OR "health gain"[tiab] OR "health gains"[tiab] OR QALYS[tiab])	323604
#17	Search (Health status[mh] OR Quality adjusted life years[mh] OR Quality of life[mh] OR "Health surveys"[mh:noexp] OR "health status indicators"[mh])	397357
#15	Search ((animals[mh] NOT (humans[mh] AND animals[mh])))	3834653
#14	Search (#13) AND ("1990"[Date - Publication] : "3000"[Date - Publication])	19195
#13	Search (#1 AND #12)	19440
#12	Search (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11)	2258983
#11	Search ("extra hepatic"[tiab] OR extrahepatic[tiab] OR "non liver"[tiab])	16032

#10	Search "observational*"[tiab]	72536
#9	Search "retrospective*"[tiab]	266444
#8	Search "follow* up"[tiab]	594094
#7	Search "case control*"[tiab]	73810
#6	Search "cross sectional"[tiab]	161603
#5	Search prospective*[tiab]	423981
#4	Search longitudinal*[tiab]	146846
#3	Search cohort*[tiab]	258785
#2	Search "Epidemiologic studies"[mh]	1550725
#1	Search (("Hepatitis C"[tiab] OR CHC[tiab] OR HCV[tiab] OR "hep C"[tiab] OR "Hepatitis C"[mh] OR "Hepatitis C, chronic"[mh]))	66687

Appendix 2: Methodological quality assessment: instrument

1. Was an appropriate comparison group used?

YES/NO

Guidance: Look for what authors matched on, but also what baseline characteristics might also affect the outcome under study.

2. Were confounders considered in analysis?

YES/NO

Guidance: e.g. stratification/matching/restriction by exclusion/adjustment

3. Was this a representative sample of the stated population of interest?

YES/NO

Guidance: Is the sample representative of the sampling frame? Is there a high participation rate? Are there described or noted differences between participants and non-participants? Is there random/stratified sampling? Note: haemophiliacs may be well represented by hundreds rather than thousands of subjects.

4. Were reliable measures of HCV status used?

YES/NO

Guidance: Is measure clearly defined? Accurately measured? Subjective or objective measurement? Are valid measures used? Are they consistently applied in both groups?

5. Were reliable measures of depression/anxiety, pain or quality of life used?

YES/NO

Guidance: Is measure clearly defined? Accurately measured? Subjective or objective measurement? Are valid measures used? Are they consistently applied in both groups?

6. Do you have concerns about the relevance of this study to the review questions?

YES/NO

Guidance: Please assess the relevance of the study, checking answers to the following questions

In particular, does the sample population have limited generalisability to a UK health service context?

Does this study describe how HCV was acquired, or particular risk factors. If the study states how HCV was acquired but very few acquired it iatrogenically, this is a problem.

Overall interpretation:

High risk of bias = Answer ‘No’ to Questions 1 AND 2

Moderate risk of bias = Studies were judged to be at a moderate risk of bias following discussion and consensus between reviewers. At a minimum, studies had to answer ‘Yes’ to Questions 1 OR 2 and ‘Yes’ to at least 4 questions in total.

Low risk of bias = Answer ‘Yes’ to all questions.

Appendix 3: Methodological quality assessment ratings

HCV and quality of life

Table A3.1: Quality of life in HCV versus general population comparison: quality assessment ratings (N=22)

Study	Risk of bias	Appropriate comparison group?	Confounders considered in analysis?	Representative sample?	Reliable measure of HCV status?	Reliable measure of quality of life?	Appropriate relevance/ generalisability?
Ashrafi et al. (2012)	HIGH	NO	NO	NO	YES	YES	NO
Bayliss et al. (1998)	HIGH	NO	NO	NO	YES	YES	NO
Bonkovsky et al. (1999)	HIGH	NO	NO	NO	YES	YES	NO
Cordoba et al. (2003)	HIGH	NO	NO	NO	YES	YES	NO
DiBonaventura et al. (2010)	HIGH	NO	NO	YES	NO	YES	NO
El Khoury et al. (2012)	HIGH	NO	NO	NO	NO	YES	NO
Foster et al. (1998)	HIGH	NO	NO	YES	YES	YES	YES
Heeren et al. (2013)	MODERATE	YES	YES	NO	YES	YES	YES
Hollander et al. (2006)	HIGH	NO	NO	NO	YES	YES	YES
Kang et al. (2005)	HIGH	NO	NO	NO	YES	YES	NO

Study	Risk of bias	Appropriate comparison group?	Confounders considered in analysis?	Representative sample?	Reliable measure of HCV status?	Reliable measure of quality of life?	Appropriate relevance/ generalisability?
Kramer et al. (2005)	HIGH	YES	NO	N0	YES	YES	YES
Kwan et al. (2008)	HIGH	NO	NO	YES	YES	YES	NO
Lowry et al. (2010)	MODERATE	YES	YES	NO	YES	YES	YES
McHutchison et al. (2001)	HIGH	NO	NO	YES	YES	YES	NO
Pattullo et al. (2011)	HIGH	NO	NO	NO	YES	YES	YES
Pojoga et al. (2006)	HIGH	YES	NO	NO	YES	YES	YES
Sinakos et al. (2010)	HIGH	NO	NO	NO	YES	YES	NO
Strauss et al. (2013)	HIGH	NO	NO	NO	YES	YES	NO
Svirtlih et al. (2008)	HIGH	NO	NO	YES	YES	YES	NO
Teixeira et al. (2006)	HIGH	NO	NO	YES	YES	YES	NO
Vietri et al. (2013)	HIGH	NO	NO	YES	NO	NO	NO
Ware et al. (1999)	HIGH	NO	YES	NO	YES	YES	NO

Low risk of bias = 'Yes' to all 6 questions; Moderate risk of bias = 'Yes' to Questions 1 or 2 and, at a minimum, 'Yes' to at least 4 criteria overall; High risk of bias = 'No' to Questions 1 and 2. Some studies were judged 'high' risk despite matching the above description for moderate, e.g. if controlling for confounding was not adequate.

Table A3.2: HCV-HIV co-infection versus HIV-infection only comparison: quality assessment ratings (N=7)

Study	Risk of bias	Appropriate comparison group?	Confounders considered in analysis?	Representative sample?	Reliable measure of HCV status?	Reliable measure of quality of life?	Appropriate relevance/ generalisability?
Briongos Figuero et al. (2011)	HIGH	NO	NO	YES	YES	YES	NO
Fleming et al. (2004)	HIGH	NO	YES	NO	YES	YES	NO
Gillis et al. (2013)	HIGH	NO	YES	NO	YES	YES	NO
Kanwal et al. (2005)	MODERATE	NO	YES	YES	YES	YES	NO
Rourke et al. (2011)	HIGH	NO	NO	YES	NO	YES	NO
Tillmann et al. (2006)	HIGH	NO	NO	NO	YES	YES	NO
Tsui et al. (2007)	HIGH	NO	YES	NO	YES	YES	NO

Low risk of bias = 'Yes' to all 6 questions; Moderate risk of bias = 'Yes' to Questions 1 or 2 and, at a minimum, 'Yes' to at least 4 criteria overall; High risk of bias = 'No' to Questions 1 and 2.

HCV and depression/anxiety: assessment of methodological quality (N=22)

Table A3.3: HCV-positive versus HCV-negative comparison: Quality assessment ratings (N=19)

Study	Risk of bias	Appropriate comparison group?	Confounders considered in analysis?	Representative sample?	Reliable measure of HCV status?	Reliable measure of depression/ anxiety?	Appropriate relevance/ generalisability?
Alavian et al. (2007)	HIGH	No	No	No	Yes	Yes	No
Ashrafi et al. (2012)	HIGH	No	No	No	Yes	Yes	No
Basseri et al. (2010)	HIGH	No	No	No	No	Yes	No
Carta et al. (2007)	MODERATE	Yes	Yes	Yes	Yes	Yes	No
Cordoba et al. (2003)	HIGH	No	No	No	Yes	Yes	No
Danoff et al. (2006)	HIGH	No	No	No	Yes	Yes	No
El-Serag et al. (2002)	HIGH	No	No	Yes	Yes	Yes	No
Erim et al. (2010)	HIGH	No	No	No	Yes	Yes	No
Gill et al. (2005)	HIGH	No	No	No	Yes	Yes	No
Goulding et al. (2001)	HIGH	No	No	No	Yes	Yes	Yes
Heeren et al. (2013)	MODERATE	Yes	Yes	No	Yes	Yes	Yes

Study	Risk of bias	Appropriate comparison group?	Confounders considered in analysis?	Representative sample?	Reliable measure of HCV status?	Reliable measure of depression/ anxiety?	Appropriate relevance/ generalisability?
Karaivazoglou et al. (2007)	HIGH	No	No	No	Yes	Yes	No
Koskinas et al. (2002)	HIGH	No	No	No	No	Yes	No
Lee et al. (2013)	HIGH	No	Yes	Yes	Yes	Yes	No
Lowry et al. (2010)	MODERATE	Yes	Yes	No	Yes	Yes	Yes
Malyszczak et al. (2010)	HIGH	No	No	No	Yes	Yes	No
Qureshi et al. (2012)	HIGH	No	No	No	Yes	Yes	No
Sun et al. (2013)	HIGH	No	No	No	Yes	Yes	No
Thein et al. (2007)	HIGH	No	No	No	Yes	Yes	No

Low risk of bias = 'Yes' to all 6 questions; Moderate risk of bias = 'Yes' to Questions 1 or 2 and, at a minimum, 'Yes' to at least 4 criteria overall; High risk of bias = 'No' to Questions 1 and 2. Some studies were judged 'high' risk despite matching the above description for moderate, e.g. if controlling for confounding was not adequate.

Table A3.4: HCV-HIV-positive versus HIV-positive comparison: Quality assessment ratings (N=4)

Study	Risk of bias	Appropriate comparison group	Confounders considered in analysis	Representative sample	Reliable measure of HCV status	Reliable measure of depression/ anxiety	Appropriate relevance/ generalisability?
Clifford et al. (2005)	HIGH	No	No	Yes	Yes	Yes	No
Thein et al. (2007)	HIGH	No	No	No	Yes	Yes	No
Von Giesen et al. (2004)	MODERATE	Yes	Yes	Yes	Yes	Yes	No
Yoon et al. (2011)	MODERATE	Yes	Yes	Yes	Yes	Yes	No

Low risk of bias = 'Yes' to all 6 questions; Moderate risk of bias = 'Yes' to Questions 1 or 2 and, at a minimum, 'Yes' to at least 4 criteria overall; High risk of bias = 'No' to Questions 1 and 2. Some studies were judged 'high' risk despite matching the above description for moderate, e.g. if controlling for confounding was not adequate.

HCV and pain

Table A3.5: Association between HCV status and pain or painful conditions: appraisal of methodological rigour (n = 26 studies)

Study	Risk of bias	Appropriate comparison group	Confounders considered in analysis	Representative sample	Reliable measure of HCV status	Reliable measure of painful condition	Appropriate follow-up period	Appropriate relevance and/or generalisability ?
Baffoni et al. (1993)	HIGH	✓			✓	✓	-	
Banks et al. (2007)	MODERATE		✓	✓	✓	✓	-	✓
Barkhuizen et al. (1999)	HIGH	✓		✓	✓		-	✓
Borque et al. (1991)	HIGH	✓			✓	✓	-	
Buskila et al. (1997)	MODERATE	✓		✓	✓	✓	-	✓
Calore et al. (2012)	HIGH	✓			✓	✓	-	
Congia et al. (1996)	HIGH			✓	✓		-	✓

Study	Risk of bias	Appropriate comparison group	Confounders considered in analysis	Representative sample	Reliable measure of HCV status	Reliable measure of painful condition	Appropriate follow-up period	Appropriate relevance and/or generalisability ?
D'Amico et al. (1996)	HIGH	✓			✓	✓	-	
De Vita et al. (2002)	HIGH				✓		-	
Gharagozloo et al. (2001)	HIGH				✓	✓	-	
Goulding et al. (2001)	HIGH				✓	✓	-	
Guennoc et al. (2009)	HIGH			✓	✓	✓	-	✓
Hsu et al. (2003)	MODERATE	✓	✓	✓	✓	✓	-	
Isaacs et al. (2013)	HIGH				✓	✓	-	
Kandemir et al. (2006)	HIGH	✓			✓	✓	-	

Study	Risk of bias	Appropriate comparison group	Confounders considered in analysis	Representative sample	Reliable measure of HCV status	Reliable measure of painful condition	Appropriate follow-up period	Appropriate relevance and/or generalisability ?
Kozanoglu et al. (2003)	HIGH	✓			✓	✓	-	
Maillefert et al. (2002)	HIGH				✓	✓	-	
Mohammad et al. (2012)	MODERATE	✓		✓	✓	✓	-	
Morasco et al. (2010)	MODERATE	✓	✓	✓	✓	✓	-	
Narvaez et al. (2005)	HIGH			✓	✓	✓	-	✓
Palazzi et al. (2008)	MODERATE	✓			✓	✓	-	✓
Rieu et al. (2002)	HIGH				✓		-	
Rivera et al. (1997)	HIGH			✓	✓	✓	-	

Study	Risk of bias	Appropriate comparison group	Confounders considered in analysis	Representative sample	Reliable measure of HCV status	Reliable measure of painful condition	Appropriate follow-up period	Appropriate relevance and/or generalisability ?
Rivera et al. (1999)	HIGH			✓	✓	✓	-	
Tsui et al. (2012)	MODERATE		✓	✓	✓	✓	✓	
Yucel et al. (2005)	HIGH	✓	✓		✓		-	

Low risk of bias = 'Yes' to all 6 questions; Moderate risk of bias = 'Yes' to Questions 1 or 2 and, at a minimum, 'Yes' to at least 4 criteria overall; High risk of bias = 'No' to Questions 1 and 2. Some studies were judged 'high' risk despite matching the above description for moderate, e.g. if controlling for confounding was not adequate.

Appendix 4: Characteristics of included studies

HCV and quality of life

Table A4.1: Studies comparing HRQOL in people with HCV and people without HCV or any other known condition

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Ashrafi et al. (2012) Iran Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**63** HCV **patients** from outpatient clinic in tertiary referral centre Mean age: 39 % male: 87	**63 control** subjects selected from community Mean age: 39 % male: 87	**Exclusions:** HBV HIV Cirrhosis Life-threatening illness Psychosis **Acquisition:** 19% Iatrogenic 51% PWID 30% unknown Liver status: non-cirrhotic **Treatment status:** 47% in treatment	**Matched:** age, gender	**HCV:** RNA **HRQOL:** SF-12	HCV patients had significantly poorer physical health summary scores (PCS) than controls. Mental health summary scores (MCS) were also poorer in the HCV group though the difference was not significant.

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
Bayliss et al. (1998) USA Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**157 HCV patients** participating in two randomised trials of interferon Mean age: 44 % male: 72	**603 well** members of US population Mean age: 44 % male: 72	**Exclusions:** HIV **Acquisition:** 36% transfusion 40.8% parenteral 23.6% other **Liver status:** 24.8% cirrhosis **Treatment status:** naïve	**Matched:** age, gender, co-morbid conditions	**HCV**: Liver biopsy **HRQOL:** SF-36	Functional health and well-being were significantly lower for HCV group compared with healthy general population on all eight SF-36 scales.
Bonkovsky et al. (1999) USA Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**284 HCV patients** in a trial of interferon Mean age: 42 % male: 73	**750 healthy** non-institutionalised adults Mean age: 42* % male: 73* ***Adjusted**	**Exclusions:** Depression HIV Decompensated liver cirrhosis Thyroid problems **Acquisition**: 43% PWID, 24% transfusion, 22% unknown, 11% other **Liver status:** 16.5%	**Adjusted:** age, gender	**HCV**: Liver biopsy **HRQOL:** SF-36	HRQOL is decreased significantly in patients with chronic HCV compared with Well-Norms … controlling for the effects of age and gender made the results more pronounced, as differences between the two samples increased slightly, and hypothesis tests remained statistically significant and

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
			cirrhosis **Treatment status:** naïve			in the same direction.
Cordoba et al. (2003) Spain Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**40 patients with chronic HCV** selected from an outpatient clinic Mean age = 55 % male = 50	**40 healthy controls** recruited through adverts, mostly relatives and hospital staff Mean age = 56 % male = 50	**Exclusions:** symptomatic co-morbidities (e.g. arthritis, migraine) **Acquisition:** 43% transfusion 2% PWID 55% unknown **Liver**: non-cirrhotic **Treatment status:** Not reported	**Matched**: age, gender, years of education	**HCV:** RNA **HRQOL:** SF-36	Only one out of eight subscales (role physical) was statistically significantly lower in the HCV group compared with control.
DiBonaventura et al. (2010) USA Risk of bias: High Route of HCV infection:	**695 respondents who reported a HCV diagnosis** in the 2009 US National	695 'Propensity matched controls' Mean age: 50 % male: 58	**Exclusions:** HBV, HIV **Acquisition**: Not reported **Liver status:** Not reported **Treatment status:** Not reported	**Matched**: age, gender, years of education, income, anxiety and depression,	**HCV:** Self-report **HRQOL:** SF-12	Compared to matched controls, respondents with HCV reported significantly worse scores in six of eight health dimensions. The other two domains (mental health and emotional role)

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
Unclear	Health and Wellness Survey Mean age: 50 % male: 58			co-morbidities, smoking, alcohol use, BMI		showed decrement in HRQOL among HCV patients, although the difference did not reach statistical significance.
El Khoury et al. (2012) USA Risk of bias: High Route of HCV infection: Unclear	**306 respondents who reported an HCV diagnosis** in the 2010 US National Health and Wellness Survey Mean age: 53 % male: 64	306 'Propensity matched controls' Mean age: 53 % male: 64	**Exclusions:** HBV, HIV **Acquisition**: Not reported **Liver status**: 3.9% cirrhosis **Treatment status:** Naïve	**Matched:** age, gender, ethnicity, education, sexual orientation, income, insurance, co-morbidities, health behaviours	**HCV:** Self-report **HRQOL:** SF-12	HCV infected patients had significantly lower PCS and MCS scores than matched controls.
Foster et al. (1998) UK Risk of bias:	**72 unselected, sequential patients with**	17 healthy laboratory and medical staff Mean age: 31	**Exclusions:** Diabetes, liver cancer, patients with multiple viral infections	**Equivalent:** age, gender	**HCV:** RNA **HRQOL:** SF-36	Compared with controls, patients with chronic HCV who had used injection drugs in the past had the

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
High Route of HCV infection: Unclear	**chronic HCV infection** attending an outpatient clinic Mean age: 39 % male: 46	% male: 53	**Acquisition**: not reported **Liver status:** non-cirrhotic **Treatment status:** not current or recent			greatest impairment in quality-of-life scores, but a reduction in quality-of-life scores was still found in patients who had never used drugs.
Heeren et al. (2013) Germany Risk of bias: Moderate Route of HCV infection: 100% iatrogenic	**20 HCV patients** attending HCV support groups Mean age: 56 % male: 0	**19 healthy relatives** accompanying patients and hospital staff Mean age: 55 % male: 0	**Exclusions:** HIV Cirrhosis Psychiatric disease History of injection drug use Shift-work Central nervous system medications **Acquisition**: 100% iatrogenic **Liver**: Non-cirrhotic **Treatment status:** Not current	**Matched**: age, gender	**HCV:** RNA **HRQOL:** SF-36	Compared to controls, HCV patients had significantly worse PCS, MCS and total summary scores.

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Hollander et al. (2006) Sweden Risk of bias: High Route of HCV infection: 100% iatrogenic	**21 unselected HCV patients** who contracted HCV iatrogenically who were starting combination treatment Mean age: 49 % male: 57	**8,930 members of general Swedish population** Mean age: 43 % male: 49	**Exclusions:** HBV, HIV, malignancies **Acquisition**: 100% blood transfusion **Liver**: Cirrhotic and non-cirrhotic **Treatment status:** Not reported	**Equivalent:** age, gender	**HCV:** RNA **HRQOL:** SF-36	HCV patients who acquired the infection iatrogenically have a marked reduction in their HRQOL compared with the general Swedish population. HRQOL among a subset of PWIDs was much worse than that found in patients who had acquired their infection iatrogenically
Kang et al. (2005) Taiwan Risk of bias: High Route of HCV infection: Unclear	**182 consecutive HCV patients** attending outpatient clinic Mean age: 60 % male: 50	**189 age- and gender-matched control subjects without HCV** Mean age: 59 % male: 56	**Exclusions:** Cirrhosis Liver cancer **Acquisition:** Not reported Liver status: Non-cirrhotic **Treatment status:** 26% recent IFN treatment	**Matched**: age, gender	**HCV:** RNA **HRQOL:** SF-36	Mean scores of general health, physical functioning, role-physical, role-emotional, vitality and mental health were significantly lower in subjects with HCV compared to control ($p<0.05$).

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
Kramer et al. (2005) Austria Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**120 patients with untreated chronic HCV** infection Mean age: 44 % male: 64	**100 age-matched healthy individuals** Mean age: 44 % male: 68	**Exclusions:** diabetes type 1, HE infections, cryoglobulinaemia **Acquisition**: transfusion 37% plasma donation 11% PWID 23% other 10% unknown 20% **Liver**: 21% cirrhotic **Treatment status:** Naïve	**Matched:** age **Equivalent:** gender	**HCV:** RNA **HRQOL:** SF-36	Patients scored significantly below population-derived normative values for all of the SF-36 domains. Role physical, role emotional and social function were most significantly impaired. There was slightly less severe impairment on the PCS than the MCS. No difference was found between previous injection drug users and other patients with respect to HRQL.
Kwan et al. (2008) USA Risk of bias: High	**N**: 303 Mean age: 53 % male: 99	**2,720 survey respondents** not reporting HCV diagnosis	**Acquisition**: Not reported **Liver**: 6% cirrhosis **Treatment status:** <12% received	**Equivalent:** gender, ethnicity, education	**HCV:** RNA **HRQOL:** SF-36	After adjusting for demographic variables and co-morbid illnesses, the authors found that HCV patients reported a

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Route of HCV infection: Unclear			therapy **Exclusions:** None - HBV and HIV status not reported			significantly lower MCS score and a trend toward a lower PCS score compared to controls.
Lowry et al. (2010) Ireland Risk of bias: Moderate Route of HCV infection: 100% iatrogenic	**20 HCV patients** recruited from hospital specialist liver clinics Mean age: 56 % male: 0	**9 healthy comparison subjects** recruited from advertisements posted in same hospital Mean age: 48 % male: 0	**Exclusions:** HBV HIV Injection drug use history Anti-depressant use history Psychiatric condition Major health problems **Acquisition**: exclusively iatrogenic **Liver**: 'mild chronic hepatitis' **Treatment status:** naïve	**Matched**: age, gender	**HCV:** RNA **HRQOL:** SF-36	HCV patients had worse scores than healthy controls for each of the eight components of the SF36 – however a significant difference was only reported for the role limitation sub-scale. (These findings were unlikely to achieve statistical significance due to the small size of the sample in this study).

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
McHutchinson et al. (2001) USA Risk of bias: High Route of HCV infection: Unclear	**905 HCV patients** in a randomised controlled trial of interferon Mean age: 44 % male: 67	**905 members of** US general population **Mean age:** Not reported **% male:** Not reported	**Exclusions:** Not reported **Acquisition**: Not reported **Liver**: Not reported **Treatment status:** Not reported	**Matched**: variables not reported	**HCV:** RNA **HRQOL:** SF-36	Statistically significantly lower SF-36 HRQOL scores for HCV patients compared with general population for five out of eight domains (physical function, role physical, general health, vitality, social function).
Pattullo et al. (2011) Canada Risk of bias: High Route of HCV infection: mixed – unclear what proportion is iatrogenic	**40 treatment-naïve, non-cirrhotic patients with HCV** rigorously screened and excluded for other causes of impaired neurocognition Mean age: 46 % male: 80	**39 healthy individuals** who were family members of the HCV patients, hospital staff and community members Mean age: 41* % male: 33* *before adjustments	**Exclusions:** HBV HIV Cirrhosis History of injection drug use in past 7 years Psychiatric disorder history Use of anti-depressants	**Adjusted:** age, years of education	**HCV:** RNA **HRQOL:** SF-36	Control subjects had higher PCS and MCS scores than patients; however a significant difference was found for PCS scores only.

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
			Major medical condition **Acquisition**: 18% past injection drug use history **Liver**: Non-cirrhotic **Treatment status:** Naïve			
Pojoga et al. (2006) Romania Risk of bias: High Route of HCV infection: Unclear	**35 HCV in-patients** referred to tertiary centres in 2002 who had been diagnosed with this disease in the previous 6 months Mean age: 42 % male: 40	**36 age and gender-matched healthy controls** Mean age: 41 % male: 33	**Exclusions:** Current PWID Alcoholic liver disease **Acquisition**: Not reported **Liver**: non-cirrhotic **Treatment status:** Not current	**Matched:** Age, gender	**HCV:** Liver biopsy **HRQOL:** SF-36	Statistically significantly lower HRQOL for HCV patients compared with controls on all SF-36 subscales

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Sinakos et al. (2010) Greece Risk of bias: High Route of HCV infection: mixed <50% iatrogenic	**99 patients with chronic HCV** Mean age: 36 % male: 65	**91 healthy controls** with paired demographic characteristics Mean age: 37 % male: 69	**Exclusions:** Other chronic diseases Liver transplantation **Acquisition:** 63% PWID **Liver**: 63%: fibrosis stage <2 **Treatment status:** Naïve	**Matched:** Age, gender	**HCV:** RNA **HRQOL:** SF-36	Patients' quality of life was found to be below that of healthy controls in all SF-36 scales – differences were significant on four of the sub-scales. The mean scores of patients remained lower than healthy controls in the majority of SF-36 scales after adjusting for the PWID.
Strauss et al. (2013) Brazil Risk of bias: High Route of HCV infection: Unclear	**35 blood donors** testing positive for HCV at donation Mean age: 37 % male: 57	**67 matched healthy blood donors** Mean age: 37 % male: 57	**Exclusions:** HBV **Acquisition**: Not reported **Liver**: Not reported **Treatment status:** Naïve	**Matched:** age, gender, race	**HCV:** RNA **HRQOL:** SF-36	Significantly lower MCS and PCS scores were found for HCV-positive blood donors when compared to matched controls. Scores were significantly lower in the HCV group for all sub-scales except physical role functioning.

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
Svirtlih et al. (2008) Serbia Risk of bias: High Route of HCV infection: Unclear	**167 hospitalised treatment-naïve patients** with HCV Mean age: 39 % male: 64	**75 controls with similar socio-demographic characteristics** Mean age: 33 % male: 52	**Exclusions:** HBV Heart failure Diabetes Psychiatric conditions 'Other co-morbidities' **Acquisition**: Not reported **Liver**: 82% non-cirrhotic **Treatment status:** Naïve	**Equivalent:** age, gender	**HCV:** RNA **HRQOL:** SF-12	Significantly lower MCS and PCS scores were found in patients with Stage 5 chronic liver disease (CLD-V) in comparison to controls.
Teixeira et al. (2006) Brazil Risk of bias: High Route of HCV infection: Unclear	**37 blood donors** identified as having mild HCV (no indication for liver biopsy) Mean age: 38 % male: 54	**37 matched healthy blood donors** Mean age: 37 % male: 54	**Exclusions:** HBV HIV **Acquisition**: Not reported **Liver status**: no liver disease **Treatment status:** naïve	**Matched:** Age, gender	**HCV:** RNA **HRQOL:** SF-36	HCV patients had significantly lower SF-36 scores when compared with matched healthy blood donors.

Study **Country** **Risk of bias** **Relevance**	**HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Vietri et al. (2013) France, Germany, Italy, Spain, UK Risk of bias: High Route of HCV infection: Unclear	**286 respondents reporting a physician diagnosis of HCV** in the European National Health and Wellness Survey 2010 Mean age: 53 % male: 58	**286 propensity matched controls** Mean age: 46* % male: 48* *prior to matching	**Exclusions:** HBV, HIV **Acquisition**: Not reported **Liver**: Not reported **Treatment status:** 12.6% current, 38.8% past	**Matched**: age, gender, country, sexual orientation, education, co-morbidities, health behaviours	**HCV:** self-reported **HRQOL:** SF-12	HCV patients also had significantly worse HRQOL than non-HCV patients on all measures (all $p < 0.001$).
Ware et al. (1999) Australia, Canada, France, Germany, Greece, Italy, Spain, UK, USA Risk of bias:	**324 HCV patients** participating in a multicentre, international RCT Mean age: 43 % male: 65	**2,467 non-institutionalised United States adults** **Mean age:** Not reported **% male:** Not reported	**Exclusions:** Decompensated cirrhosis HIV Organ transplantation Psychiatric conditions Seizure disorders Cardiovascular	**Adjusted:** age, gender, ethnicity	**HCV:** RNA **HRQOL:** SF36	Chronic hepatitis C patients were impaired in 5 of 8 SF-36 concepts (physical functioning, role-physical, general health, vitality and social functioning) in comparison with matched population norms.

Study Country Risk of bias Relevance	HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
High Route of HCV infection: mixed <50% iatrogenic			disease Renal insufficiency Haemoglobinopathy Haemophilia Poorly controlled diabetes Immunologically mediated diseases **Acquisition**: 27% transfusion, 40% PWID, 33% unknown **Liver:** 3% cirrhosis **Treatment status:** previous interferon treatment			

Table A4.2: Studies comparing HRQOL in people co-infected with HCV and HIV and people with HIV only

Study **Country** **Risk of bias** **Relevance**	**HIV/HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Briongos Figuero et al. (2011) Spain HIGH Route of HCV infection: Mixed	**N** =71 Mean age = 44 % male = 75 **Recruitment:** HIV-infected patients under follow-up at hospital clinic identified as HCV+	N =79 **Recruitment:** as for co-infected group, but not identified as HCV+	**Risk category:** 35.3% heterosexual contact, 18.7% MSM, 38% PWID, 8% unknown **Liver** = not reported **Treatment status** = 84% ART (current) **Excluded co-morbidities:** Physical/mental condition that made interviewing problematic 'Being frequently seen by specialist' Comorbidity not reported separately for the HIV-HCV co-infected group	**Equivalent**: not reported **Adjusted:** Age Sex Depression ART regimen Symptomatic (yes/no)	**HCV:** not reported **HRQOL:** MOS-HIV Full	Patients with HIV/HCV co-infection had lower scores in General Health Perceptions, Pain, Physical Functioning, Social Functioning and physical health scores. Logistic regression found lack of a HCV diagnosis was a protective variable against poor mental health scores.

Study Country Risk of bias Relevance	HIV/HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
Fleming et al. (2004) USA HIGH Route of HCV infection: Mixed	**N** = 136 Mean age = 46 % male = 76 **Recruitment** HIV-infected patients at hepatology and infectious disease clinics with detectable HCV RNA	**N** = 53 **Recruitment:** as for co-infected group, but not identified as HCV antibody and RNA positive	**Risk category:** 89% PWID, 8% MSM, 3% other **Liver** = not reported **Treatment status** = 75% ART (current) **Excluded co-morbidities:** None (HBV status not reported) 77% of HCV group had 'active medical comorbidities'	**Equivalent:** Age; sex **Adjusted:** Age Risk factor US born Education Stable housing Income Employment PWID (any) Methadone (ever) Alcohol (12 months) Ongoing HAART therapy HCV (time since diagnosis, RNA load, ChildPugh score Depression Karnofsky score	**HCV:** taken from medical records **HRQOL:** Hepatitis Quality of Life questionnaire Full	Scores were statistically similar for patients infected with HIV alone or with HIV/HCV co-infection. After adjustment, HRQOL was not affected by HCV co-infection, although analysis of interaction effects suggested that co-infection had a negative impact on MCS for patients with high Karnofsky scores and for those with a history of depression.

Study **Country** **Risk of bias** **Relevance**	**HIV/HCV cohort**	**Comparison group**	**Nature of HCV infection**	**Matching/ equivalence**	**HCV measure/ HRQOL measure**	**Findings**
Gillis et al. (2013) Canada HIGH Route of HCV infection: Mixed	**N** = 131 Mean age = 46 % male = 82 **Recruitment:** people enrolled in a regional cohort study (Ontario Regional Treatment Network OCS) at 4 HIV care sites who were identified as HCV+ (by antibody, RNA, diagnosis or adverse event)	**N** = 964 **Recruitment:** as for co-infected group, but not identified as HCV+	**Risk category:** 41% PWID, 44% MSM, 9% endemic country **Liver** = not reported **Treatment status**: 5% on HCV medication; 85% ART (current) **Excluded co-morbidities:** HBV 43% of HCV group had depression score (CES-D) >16	Equivalent Age; sex Adjusted Age Sex Income PWID as a risk factor MSM as a risk factor Recent drug use Frequency of drinking 6 plus alcoholic drinks Current smoking status Depression (PCS only)	**HCV:** from medical records **HRQOL:** SF-36 v.2 summary scores only (PCS and MCS)	Physical and mental HRQOL was lower in HIV-HCV co-infected individuals compared to mono-infected individuals. After adjustment, the negative impact of HCV remained significant for PCS only.
Kanwal et al. (2005) USA	**N** = 279 **Age** (mode) = 35-39	**N** = 1,493 **Recruitment:** as for co-	**Risk category:** 49% PWID, 36% MSM, 11% heterosexual contact,	**Equivalent:** Age, sex, income **Adjusted:**	**HCV:** taken from medical records	No significant differences were seen between

Study Country Risk of bias Relevance	HIV/HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
MODERATE Route of HCV infection: Mixed	% male = 80 **Recruitment:** subset of national sample of adults with HIV receiving care in USA (those providing baseline and follow-up data in a 9-month trial who were identified as HCV+ by antibody, RNA or diagnosis)	infected group, but not identified as HCV+	10% other **Liver** = not reported **Treatment status:** 85% ART (ever) **Excluded co-morbidities:** HBV 57% of HCV group had one or more medical comorbidity 41% of HCV group were classed as depressed	Age Sex Ethnicity Education Living with spouse Income Employment Insurance type Risk factor HIV-related variables Depression (for PHS only) Other co-morbidity	**HRQOL:** HCSUS HRQOL survey. PHS and MHS summary scores only	patients with HIV-HCV co-infected and HIV mono-infected individuals. The results did not change after adjustment.
Rourke et al. (2011) Canada HIGH Route of HCV infection: Mixed	**N** = 95 Mean age = 44 % male = 73 **Recruitment:** subset of regional	N = 387 **Recruitment:** as for co-infected group, but not self-identified as	**Risk category:** 71% substance use (last 12 months) **Liver** = not reported Treatment status 74% ART (ever)	**Equivalent:** Age, sex No adjustments	**HCV:** self-report **HRQOL:** MOS-HIV Full	Compared with individuals infected with HIV only, HIV-HCV co-infected individuals reported

Study Country Risk of bias Relevance	HIV/HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
	sample of adults with HIV receiving AIDS services in Ontario (those providing follow-up data in a cohort who self-identified as HCV+ and as not 'clear of the infection')	HCV+, or as having cleared the infection	**Excluded co-morbidities:** None (HBV status not reported) Comorbidity not reported separately for the HIV-HCV co-infected group (47% of all those in the study were 'significantly depressed')			significantly poorer health-related quality of life in both physical and mental health summary measures.
Tillmann et al. (2006) Germany HIGH Route of HCV infection: Mixed	**N** = 35 **Mean age** = not reported **% male** = not reported (82% in study as a whole) **Recruitment:**	**N** = 154 **Recruitment:** as for co-infected group, but identified as HCV antibody negative	**Risk category**: not reported separately for groups (risk categories for study as a whole = 14% PWID, 56% MSM, 13% heterosexual contact, 4% haemophilia, 2% contaminated blood, 3%	Equivalence not reported Adjusted Age Employment HBV status (anti-HBc, HBsAg status) HIV measures (viral	**HCV:** taken from medical records **HRQOL:** HIV-SELT Summary score only	Patients co-infected with HIV and HCV showed significantly impaired quality of life in comparison to patients with HIV infection only.

Study Country Risk of bias Relevance	HIV/HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
	Not reported. Described as a cohort of HIV-infected patients who had also tested HCV antibody positive		endemic country, 9% other) **Liver** = not reported Treatment status: not reported **Excluded co-morbidities:** None (HBV status not reported) Comorbidity not reported for the HCV group, or for study as a whole	load, CD4 cell count, CDC stage, time since diagnosis)		After adjustment, anti-HCV status was found to be a relevant parameter, but slightly less so than employment.
Tsui et al. 2007 USA HIGH Route of HCV infection: Mixed	**N** = 142 Mean age = 42 % male = 81 **Recruitment:** subset of San Francisco-based REACH cohort	**N** = 74 **Recruitment:** as for co-infected group, but identified as HCV antibody	**Risk category**: 45% current PWID **Liver** = not reported **Treatment status:** 16% ART (current) **Excluded co-**	**Equivalent:** Age; sex; ethnicity **Adjusted:** Age Sex Ethnicity Current HAART	**HCV:** tests of HCV antibody and RNA **HRQOL:** SF-36 v.2 summary scores only	Individuals co-infected with HIV and HCV had significantly lower mean scores in the domains of physical

Study Country Risk of bias Relevance	HIV/HCV cohort	Comparison group	Nature of HCV infection	Matching/ equivalence	HCV measure/ HRQOL measure	Findings
	of homeless and marginally housed individuals with HIV (those agreeing to HCV testing and identified as HCV antibody positive)	negative	**morbidities:** Where HBV status not reported 33% of HCV group had a 'comorbid medical condition'	therapy CD4 count Current substance use (PWID, Crack, alcohol) Co-morbidity (current) Drug treatment (past year) Insured On disability Regular healthcare provider Homeless in past year		functioning, bodily pain, social functioning and role limitation. After adjustment, co-infection was associated with a lower physical component score, but not a lower mental component score.

HCV and depression/anxiety

Table A4.3: Studies comparing depression/anxiety in HCV-positive versus HCV-negative groups (n=19)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
Alavian et al. (2007) Iran HIGH Route of HCV infection: Unknown	**14 hepatitis patients** from hospital clinic Mean age (SD): 44.0 (8.3) Male: 93%	**64 healthy volunteer blood donors** Mean age (SD): 38.4 (10.7) Male: 67%	**Exclusions:** No exclusion criteria reported **Acquisition:** Not described Liver disease status: Not described **Alcohol use:** Not described **IV Drug use:** Not described **Treatment status:** Not described **History of psychiatric or neurocognitive disorder:** Not reported **Co-infections:** Not reported	**Matched on:** Age, gender, education **Imbalances between groups:** No difference reported but looks fairly large **Adjusted for in analysis:** No	Anti-HCV antibody positive for at least six months **Depression/ Anxiety:** Hospital Anxiety and Depression Score (HADS)	**Depression (HADS)** Mean scores HCV+ patients: 6.4 (3.7) Healthy controls: 4.7 (2.4) $p<0.001$ **Anxiety (HADS)** Mean scores (SD) HCV+ patients: 9.5 (3.8) Healthy controls: 4.8 (2.4) $p<0.05$ Summary: statistically significant difference (SSD) between groups on measures of depression and anxiety.

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
Ashrafi et al. (2012) Iran HIGH Route of HCV infection: Mixed	**63 patients from outpatient clinic** in tertiary referral centre Mean age (SD): 39 (11) Male: 54%	**63 subjects selected from the community** Mean age (SD): 39 (11)	**Exclusions:** Serious/ life threatening co-morbidities Cirrhosis Psychosis Concomitant HIV infection **Acquisition:** Reported transmission routes: 51% PWID 19% blood products 30% unknown Liver disease status: Metavir rating 0-3: 78% Grading of mild/minimal/ moderate: 76%	**Matched on:** Age and gender **Imbalances between groups:** None reported **Adjusted for in analysis:** Not reported	**HCV:** HCV diagnosis based on American Association for Study of Liver Disease (i.e. HCV-RNA PCR positive) **Depression/ Anxiety:** Hospital Anxiety and Depression Scale (HADS)	**Depression (HADS)** Median (IQR) HCV+ patients: 6 (2,9) Community controls: 5 (3,8) **Anxiety (HADS)** Median (IQR) HCV+ patients: 7 (5,11) Community controls: 8 (7,10) Non-statistically significant difference (nSSD) Summary: depression scores higher for HCV+ patients but anxiety scores higher for community controls; however finding may not be representative of findings in the 'true' population (because nSSD).

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			Alcohol use: Not described **Treatment status:** Not reported **History of psychiatric or neurocognitive disorder:** Not reported **Co-infections:** Not reported			
Basseri et al. (2010) USA HIGH Route of HCV infection: Unknown	**800 HCV patients from tertiary care clinic** Mean age (SD): 48.5 (0.4) Male: 57%	**Unknown number of controls** from studies using US population data Mean age (SD): 44.0 (0.5) Male: 47-50%	**Exclusions:** Not reported **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** Not reported **IV drug use:** 46.8% PWID – sample. Not	**Matched on:** Not reported **Imbalances between groups:** Not reported **Adjusted for in analysis:** Not reported	**HCV:** Not reported **Depression/ Anxiety:** Not reported	Depression OR 3.55 (95% CI 2.99, 4.21) Summary: Odds of HCV patients having depression 3.55 times more likely than in US population; this result is statistically significant.

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			reported for comparison **Treatment status:** Not reported **History of psychiatric or neurocognitive disorder:** Not reported **Co-infection:** 5.3% HIV-infected			
Carta et al. (2007) Italy MODERATE Route of HCV infection:	**135 HCV patients from Liver Unit at university hospital** Mean age (SD): 50.7 (10.3)	**540 subjects randomly selected** from previous epidemiological survey of health conditions Mean age (SD):	**Exclusions:** Previous interferon (IFN) treatment Co-infected with HBV or HIV Lifetime drug or alcohol addiction	**Matched on:** Age and gender **Imbalances between groups:** None reported **Adjusted for**	**HCV:** Not described **Depression/ Anxiety:** Composite International Diagnostic Interview from	**Major depressive disorder** HCV+ patients = 44/135 (32.6%) Comparison group = 69/540 (12.8%) OR 3.3 (95% CI 2.1, 5.1) **Generalized Anxiety**

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
Unknown	Male: 61%	50.1 (11.2) Male: 61%	Lifetime malignancies **Acquisition:** Not reported **Liver disease status:** Not reported **Treatment status:** Naïve **History of psychiatric or neurocognitive disorder:** Not reported	**in analysis:** Not reported	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (CIDI-DSM-IV) Major depressive disorder Generalized Anxiety Disorder Panic Disorder Social Phobia	**Disorder** HCV+ patients = 13/135 (9.6%) Comparison group = 49/540 (9.1%) OR 1.1 (95% CI 0.02, 504.5) **Panic Disorder** HCV+ patients = 12 (8.9%) Comparison group = 15 (2.8%) OR 3.4 (95% CI 1.5, 7.5) **Social Phobia** HCV+ patients = 3 (2.2%) Comparison group = 24 (4.4%) OR 0.5 (95% CI 0.1, 2.1) Summary: HCV patients are significantly more likely than comparison population to have depression and anxiety disorders.

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
Cordoba et al. (2003) Spain HIGH Route of HCV infection: Mixed	**40 HCV patients from hospital outpatient clinic** Mean age (SD): 55y (6) Male: 50% Education (SD): 7.5y (2.2)	**40 relatives of patients or hospital employees** Mean age (SD): 56y (6) Male: 50% Education (SD): 7.5y (2.4)	**Exclusions:** Marked cognitive disorder Impaired autonomy Significant alcohol consumption Illiteracy Hospital admission in past 3 months Symptomatic co-morbidities (arthritis, migraine, back pain) **Acquisition:** 43% Blood transfusion, 2% PWID, 55% Unknown **Liver disease:** AST score (SD): 45 (27) ALT score (SD): 66 (48)	**Matched on:** Age, gender, education **Imbalances between groups:** None **Adjusted for in analysis:** Not applicable	**HCV:** HCV antibody HCV RNA **Depression/ Anxiety:** Beck Depression Inventory (BDI) State Trait Anxiety Inventory (STAI)	**Median Depression (IQR):** HCV group: 9 (3-13) Comparison group: 3 (0.5-8) **Mean Depression (SD):** HCV group: 8 (6) Comparison group: 5 (5) **Median Anxiety (IQR):** HCV group: 17 (12-28) Comparison group: 16 (9-22) **Mean Anxiety (SD):** HCV group: 19 (11) Comparison group: 16 (9)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			Treatment status: Pre-treatment **Co-infection status:** Not reported			
Danoff et al. (2006) USA HIGH Route of HCV infection: Unknown	**112 men recruited from gastro-enterology clinic** and primary care of Veterans Healthcare system **Age:** Not reported **Male:** 100%	**239 control subjects seen in the same clinics** **Age:** Not reported **Male:** 100%	**Exclusions:** Cirrhosis IFN or other treatment within past 6 months HIV co-infection >3 alcoholic drinks/day Using illicit drugs Taking methadone Prostate cancer or surgery Renal failure Thyroid disease Medications to affect sexual function	**Matched on:** No matching **Imbalances between groups:** Comparison more likely to be older and ethnic minorities but no data reported **Adjusted for in analysis:** Not reported	**HCV:** Positive HCV antibodies and detectable HCV-RNA **Depression/ Anxiety:** Beck Depression Inventory (BDI)	**Depression (BDI)** HCV+ patients: Mild: 25/112 (22.3%) Moderate: 22/112 (19.6%) Severe: 6/112 (5.4%) Control group: Mild: 51/239 (21.3%) Moderate: 5/239 (2.1%) Severe: 1/239 (0.4%) SSD differences between groups on mild, moderate and severe measures of depression (p<0.001) Summary: Statistically significant differences between HCV-positive

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			Acquisition: Not reported **Liver disease status:** Not reported **Treatment status:** Not reported **History of psychiatric or neurocognitive disorder:** Not reported			patients and non-HCV control subjects for all measures of severity of depression.
El-Serag et al. (2002) USA HIGH Route of HCV infection: Unknown	**22,341 Vietnam veterans** selected from Veterans Hospitals system patient record files **Mean age (SD):** 43.87	**43,267 non-HCV control subjects from same source** **Mean age (SD):** 48.28 (7.83) **Male:** 97.94% **Ethnicity:** Caucasian 68.98%	**Exclusions:** None reported **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** 77.62% -sample 45.95% - comparison	**Matched on:** Year of admission to hospital **Imbalances between groups:** Not equivalent on age, ethnicity **Adjusted for**	**HCV:** HCV RNA (ICD-9 diagnosis) **Depression/ Anxiety:** Diagnostic and Statistical Manual of Mental Disorders, 4th	**Depression (DSM-IV)** HCV+ patients: 11,049/22,341 (49.6%) HCV- controls: 16,923/43,267 (39.11%) Adjusted RR 1.24 (95% CI 1.20, 1.28) **PTSD (DSM-IV)** HCV+ patients: 7,491/22,341

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
	(4.87) **Male:** 99.06% **Ethnicity:** Caucasian 58.92%		**IV Drug use:** 69.4% - sample 31.13% - comparison **Treatment status:** Not currently treated with IFN **History of psychiatric or neurocognitive disorder:** Not reported **Co-infection status:** Not reported	**in analysis:** Yes	Edition (DSM-IV) diagnosis of depression, post-traumatic stress disorder (PTSD), anxiety	(33.53%) HCV- controls: 10,598/43,267 (24.49%) Adjusted RR 1.39 (95% CI 1.34, 1.49) **Anxiety (DSM-IV)** HCV+ patients: 9,115/22,341 (40.8%) HCV- controls: 14,245/43,267 (32.92%) Adjusted RR 1.15 (95% CI 1.11, 1.97) Summary: Patients with HCV are statistically significantly more likely to be depressed, have PTSD or anxiety than similar patients without HCV.
Erim et al. (2010) Germany	**81 HCV-positive patients** seen at hepatitis	**86 normative participants without health**	**Exclusions:** Cirrhosis **Current IFN treatment:** HBV or	**Matched on:** No matching **Imbalances**	'with HCV' not further described	**Depression (BDI)** Mean (SD) HCV+ patients: 10.1 (9.7)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
HIGH Route of HCV infection: Mixed	outpatient unit of university hospital Mean age (SD): 47.1 (11.9) Male: 63%	**problems (BDI)** Mean age (SD): 55 (16.1) **Male:** 37.2% **152 normative participants without health problems (HADS)** Mean age (SD): 42 (15.4) Male: 38%	HIV co-infection **Acquisition:** 39.5% iatrogenic 9.9% drug use 2.5% sexual contact 14.8% medical work 33.3% unknown **Liver disease status:** No cirrhosis (excluded) **Alcohol use:** Not reported **Treatment status:** 49.4% previous IFN therapy; of which 30% terminated IFN due to side effects **History of psychiatric or neurocognitive**	**between groups:** Age and gender **Adjusted for in analysis:** Not reported	**Depression/ Anxiety:** Beck Depression Inventory (BDI) Hospital Anxiety and Depression Scale (HADS)	BDI normative: 6.45 (5.2) *p*=0.001 **Depression (HADS (D))** Mean (SD) HCV+ patients: 5.41 HADS normative: 4.4 *p*<0.001 **Anxiety (HADS (A))** Mean (SD) HCV+ patients: 7.17 (4.0) HADS normative: 5.8 (3.2) *p*<0.003 Summary: Depression and anxiety were statistically significantly associated with HCV-positive status.

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			disorder: 25.9% previous psychiatric treatment			
Gill et al. (2005) Pakistan HIGH Route of HCV infection: Unknown	**98 HCV patients at international hospital** Mean age (SD): 45 (15) **Male:** 58.2%	**100 healthy relatives accompanying patients or hospital staff** **Mean age (SD):** 30.16 (11.19) **Male:** 40.0%	**Exclusions:** Not reported **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** Not reported **IV Drug use:** Not reported **Treatment status:** Not reported **History of psychiatric or neurocognitive disorder:** Not reported Co-infection: 'Tested	**Matched on:** Not reported **Imbalances between groups:** Not described but looks imbalanced for age and gender **Adjusted for in analysis:** Not described	**HCV:** HCV-RNA PCR **Depression/ Anxiety:** Beck Anxiety Inventory (BAI) – Mean/ Moderate/ Severe	**Mean Anxiety (BAI)** Mean (SD) HCV+ patients: 20.2 (13.62) Comparison: 14.3 (8.0) *p*<0.001 **Moderate anxiety (BAI)** HCV+ patients: 32/98 (32.7%) Comparison: 8/100 (8%) *p*<0.001 **Severe anxiety (BAI)** HCV+ patients: 16/98 (16.3%) Comparison: 0/11 (0%) *p*<0.001 Summary: HCV+ patients were more likely than their accompanying relatives or

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
			for HBV and HIV co-infection' but no data reported			hospital staff to experience more anxiety, and more moderate and severe anxiety.
Goulding et al. (2001) Ireland HIGH Route of HCV infection: Mixed	**49 patients from hospital hepatology unit** Mean age (SD): 48 (7.19) Male: 21%	**25 healthy volunteers;** relatives accompanying patients to GP or other patients attending for routine medical check-ups for work Mean age (SD): 38 (13) Male: 24%	**Exclusions:** History of alcohol use IFN treatment HBV co-infection **Acquisition:** 64% infected via anti-D immunoglobulin 33% infected by IV drug use 4% infected via blood transfusions **Liver disease status:** Not reported **IV Drug use:** Not reported **History of**	**Matched on:** Age and gender **Imbalances between groups:** Not described but appears non-equivalent on age **Adjusted for in analysis:** Not reported	**HCV:**HCV-RNA **Depression/ Anxiety:** Hospital Anxiety and Depression Scale (HADS)	**Depression (HADS)** Mean score HCV+ patients: 7.41 Comparison: 2.83 *p*<0.001 **Anxiety (HADS)** Mean score HCV+ patients: 11.15 Comparison: 7.25 *p*<0.0001 Summary: HCV+ patients infected by contaminated anti-D immunoglobulin were significantly more likely to score higher on measures of depression and anxiety in

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			psychiatric or neurocognitive disorder: Not reported			comparison to accompanying relatives or other patients attending GP medical check-ups.
Heeren et al. (2013) Germany MODERATE Route of HCV infection: Iatrogenic	**20 HCV+ patients attending HCV support groups** Mean age (SD): 56.8 (4.2) Male: 0%	**19 relatives accompanying patients and hospital staff** Mean age (SD): 55.3 (4.2) Male: 0%	**Exclusions:** Cirrhosis History of PWID History of shift work IFN treatment Current neurological/psychiatric disease Current medication with CNS effect **Acquisition:** 100% infected with contaminated anti-D 100% 30+ years since HCV infection	**Matched on:** Age and gender **Imbalances between groups:** Not reported but alcohol intake looks non-equivalent **Adjusted for in analysis:** Not reported	**HCV:** HCV-RNA positive PCR positive/ negative **Depression/ Anxiety:** Hospital Anxiety and Depression Scale (HADS) Beck Depression Inventory (BDI)	**Depression (HADS)** Median (IQR) HCV+ patients: 10.0 (6.25-12.00) Comparison group: 1 (0.00-4.0) $p<0.001$ **Anxiety (HADS)** Median (IQR) HCV+ patients: 11.5 (9.0-14.75) Comparison group: 5 (2.0-6.0) $p<0.001$ **Depression (BDI)**

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			Alcohol use: Light-moderate alcohol intake: 45%-sample 74%-comparison **Co-infection:** Not reported			Median (IQR) HCV+ patients: 16.5 (8.5-26.0) Comparison group: 5 (2.0-11.0) *p*<0.001 Summary: Depression and anxiety were more likely to be reported in women with HCV than in accompanying relatives and clinic staff.
Karaivazoglou et al. (2007) Greece HIGH Route of HCV infection:	**32 HCV+ patients** recruited from university hospital Mean age (SD): 48.6 (15.5), range 43.0 to 54.2	20 randomly recruited relatives of patients and hospital staff Mean age (SD): 49.7 (15.0), range 42.7 to 56.7	**Exclusions:** Cirrhosis PWID or alcohol use past 12 months Current IFN treatment or psychotropic treatment past 12	**Matched on:** No matching **Imbalances between groups:** Age, educational level, severity of depression, fatigue	**HCV:** HCV-RNA HCV-PCR **Depression/ Anxiety:** Beck Depression Inventory (BDI)	**Depression severity (BDI)** Mean (SD), range HCV+ patients: 8.8 (7.7), 6.0 to 11.5 Comparison: 8.9 (7.6), 5.4 to 12.5 *p*=0.500 Summary: No statistically

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
Unknown	Male: 53%	Male: 50%	months Stroke, cancer, cerebrovascular disease, mental retardation, dementia, seizure disorder, other liver disease, hepatic encephalopathy **Acquisition:** Not reported **Co-infection:** Not reported	**Adjusted for in analysis:** Not in baseline associations		significant differences between groups in terms of depression severity; however in this study depression is being analysed as a potential confounder for neurocognitive function.
Koskinas et al. (2002) Greece HIGH Route of HCV infection:	**38 HCV+ patients at an outpatient internal medicine clinic** Mean age	**58 individuals in same setting** who had no chronic disease and had undergone cholecystectom	**Exclusions:** History of mental illness Alcohol >10g/day **Acquisition:** Not reported	**Matched on:** No matching **Imbalances between groups:** Age	**HCV:** Not reported **Depression/ Anxiety:** Zung Self-rating Depression	**Depression (SDS)** Median (range) HCV+ patients: 34.4 (26.3-67.5) Comparison: 35.6 (27.5-61.3) P=0.073 Summary: No significant

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
Unknown	(range): 43 (25-60) Male: 68%	y Mean age (range): 57 (19-81) Male: 40%	**Liver disease status:** Not reported **Alcohol use:** Not reported (excluded high consumption) **IV Drug use:** Not reported **Treatment status:** Measures taken prior to IFN treatment Co-infection: Not reported	**Adjusted for in analysis:** Not reported	Scale (SDS)	differences in depression scores between HCV+ patients and cholecystectomy patients in the same setting who had no other chronic conditions. Unknown proportion of iatrogenically infected versus PWID HCV patients. Quite possible comparison group was also slightly depressed!
Lee et al. (2013) USA HIGH Route of HCV infection: Unknown	**178 HCV-positive patients** identified through national survey (NHANES) Mean age (SD):	**9,178 HCV-negative participants from same survey** Mean age (SD): 49 (0.44) **Male:** 50%	**Exclusions:** Cancer HIV infection Hepatotoxic medication Pregnant **Acquisition:** Not reported	**Matched on:** No matching **Imbalances between groups:** Gender, PWID, excessive alcohol use	**HCV:** HCV-RNA (RIBA) **Depression/ Anxiety:** Patient Health Questionnaire 9 (PHQ-9)	**No Depression (PHQ-9)** HCV+ patients: 80/178 (45.1%) Comparison: 6672/9178 (72.7%) **Mild Depression (PHQ-9)** HCV+ patients: 77/178 (43.2%)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
	48.8 (0.67) **Male:** 69.4%		**Liver disease status:** Not reported **Alcohol use:** 77.7% **IV Drug use:** 47.6% **Treatment status:** Not reported **History of psychiatric or neurocognitive disorder:** Not reported **Co-infection:** Not reported	**Adjusted for in analysis:** Yes but not for PWID or alcohol		Comparison: 2239/9178 (24.4%) **Major Depressive Disorder (PHQ-9)** HCV+ patients: 20/178 (11.4%) Comparison: 257/9178 (2.8%) **Contemplation of suicide (PHQ-9)** HCV+ patients: 1/178 (1%) Comparison: 10/9178 (0.1%) **Depression** OR 1.93 (95% CI 1.17, 3.17) Summary: People with HCV were significantly more likely to be depressed in comparison to those without HCV, even when confounding variables including PWID and alcohol use are taken into account.

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
Lowry et al. (2010) Ireland MODERATE Route of HCV infection: iatrogenic	**20 HCV+ patients recruited from hospital specialist liver clinics** PCR-positive Mean age (SD): 54.1 (10.6) PCR-negative Mean age (SD): 57.7 (4.3) Male: 0%	**9 comparison subjects recruited from advertisements posted in same hospital** Mean age (SD): 48.3 (9.1) Male: 0%	**Exclusions:** Lifetime substance use Co-infection HBV or HIV Psychiatric diagnosis past three years Anti-depressants past three years History of: brain injury, thyroid dysfunction, co-morbid health problems, illiteracy **Acquisition:** 100% iatrogenically infected **Liver disease status:** 100% mild-minimal liver fibrosis	**Matched on:** Age and gender **Imbalances between groups:** Education **Adjusted for in analysis:** Yes	**HCV:** HCV-PCR **Depression/ Anxiety:** Hospital Anxiety and Depression Scale (HADS)	**Depression (HADS)** Mean (SD) PCR+ group: 6.55 (5.6) PCR- group: 4.4 (3.09) Comparison group: 2.4 (2.40) *p*>0.05 (non SSD) **Anxiety (HADS)** Mean (SD) PCR+ group: 4.18 (3.8) PCR- group: 7.78 (4.71) Comparison group: 6.00 (2.69) *p*>0.05 (non SSD)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
			55% HCV-viraemic 45% spontaneous clearance **Treatment status:** 100% untreated			
Malyszczak et al. (2010) Poland HIGH Route of HCV infection: Unknown	**48 HCV+ patients from internal, haematological and infectious disease hospital wards** prior to IFN treatment Mean age (range): 48.5 (22-65) Male: 52%	**45 healthy controls** from unknown setting Mean age (range): 48.8 (20-82) Male: 51%	**Exclusions:** Psychotic state Unconsciousness or dementia **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** Not reported **IV Drug use:** Not reported **Treatment status:** Not reported **Co-infection:** Not	**Matched on:** No matching **Imbalances between groups:** None **Adjusted for in analysis:** Not reported	**HCV:** HCV+ not further described **Depression/ Anxiety:** Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)	**Depression (DSM-IV)** Mean (SD) HCV+ patients: 3.93 (0.72) Comparison: 1.93 (0.72) Adjusted F= 2.65 *p*= 0.054 **Depression Score - Men (DSM-IV)** Mean (SD) HCV+ patients: 3.5 (1.07) Comparison: 1.52 (1.04) **Depression Score - Women (DSM-IV)** Mean (SD)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
			reported			HCV+ patients: 4.35 (0.95) Comparison: 2.36 (0.97) **Mean Diagnosis Depression (DSM-IV)** HCV+ patients: 7/48 (15.2%) Comparison: 1/45 (2.2%) Summary: Statistically significant effect for depression in HCV+ patients compared to healthy controls.
Qureshi et al. (2012) Pakistan HIGH Route of HCV infection: Unknown	**95 HCV+ patients attending a hospital gastro-enterology outpatient clinic** Age range (y):	**82 people attending with the patients** Age range: 21-35: 20% 36-50: 57% >50: 22% Male: 47%	**Exclusions:** Cirrhosis or liver failure IFN treatment Anti-depressant therapy Other psychiatric illness (neurological disorder or severe	**Matched on:** Age and gender **Imbalances between groups:** None reported **Adjusted for in analysis:**	**HCV:** HCV serologic markers **Depression/ Anxiety:** Hospital Anxiety and Depression Scale (HADS)	**Total depression (HADS)** HCV+ patients: 69/95 (72.6%) Comparison: 31/82 (37.8%) $p<0.001$ **No depression (HADS)** HCV+ patients: 26/95 (27.36%) Comparison: 51/82 (62.19%)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
	21-35: 15% 36-50: 50% >50: 35% Male: 43%		depression) Severe chronic illness Liver disease of non-HBV or -HCV aetiology **Acquisition:** Not reported **Alcohol use:** Not reported **IV Drug use:** Not reported	None reported		*p*<0.001 **Mild depression (HADS)** HCV+ patients: 50/95 (52.6%) Comparison: 27/82 (32.9%) *p*<0.001 **Moderate-severe depression (HADS)** HCV+ patients: 19/95 (20%) Comparison: 4/82 (4.87%) *p*<0.001 Summary: HCV+ patients are significantly more likely than their attendants to experience depression, regardless of its severity.
Sun et al. (2013) USA HIGH Route of	**19 HCV+ patients from gastro-enterology clinics** at	**28 healthy controls** Mean age (SD): 56.6 (4.5) **Male:** 100%	**Exclusions:** Cirrhosis PWID Other chronic	**Matched on:** Age, gender, ethnicity **Imbalances between**	**HCV:** HCV-RNA **Depression/ Anxiety:** Beck Depression Inventory (BDI)	**Depression (BDI)** Mean (SD) HCV+ patients: 6.7 (6.0) Comparison: 5.4 (4.1)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching/ Equivalence**	**Measure of Hep C status** **Measure of depression / Anxiety**	**Results**
HCV infection: Unknown	Veterans Affairs Medical Centre **Age y (SD):** 53.2 (6.0) **Male:** 100%		infections >20g alcohol/day IFN treatment past 4 years Diagnosed depression or other significant psychiatric disease Seizure disorders History of head injury **Acquisition:** Not reported **Liver disease status:** No cirrhosis patients (excluded) **IV Drug use:** 63% history of drug use	**groups:** Education **Adjusted for in analysis:** Yes		*p*<0.01 Summary: No statistically significant difference in depression between HCV+ patients and healthy controls.
Thein et al. (2007) Australia HIGH	**19 HCV+ pre-treatment patients** recruited from	**30 university population** recruited through	**Exclusions:** No previous HCV treatment PWID	**Matched on:** Gender and education **Imbalances**	**HCV:** HCV-RNA **Depression/ Anxiety:** Depression and	**Depression (DASS)** Mean (95% CI) HCV+: 7.79 (4.94-10.64) Comparison: 5.33 (4.84-5.83)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
Route of HCV infection: Mixed	tertiary level hepatitis clinic for drug trial Mean age (SD): 42.6 (6.5) **Male:** 63.2%	advertisements Mean age (SD): 34.8 (8.2) **Male:** 100%	Alcohol intake >100g/week Cirrhosis Hepatocellular carcinoma Non-HCV chronic liver disease History neurological disorders Active infection CD4 count <200 **Acquisition:** Not reported **Liver disease status:** 84.2% F0-F2 stage liver disease **Alcohol use:** 21.0%>= 5 alcoholic drinks past month **IV Drug use:**	**between groups:** Comparison group younger **Adjusted for in analysis:** Yes	Anxiety Stress Scales (DASS)	*p*=0.065 **Anxiety (DASS)** Mean (95% CI) HCV+: 5.16 (3.42-6.90) Comparison: 5.43 (4.61-6.25) *p*=0.564 Summary: Neither depression nor anxiety were significantly associated with HCV mono-infected compared to a healthy population.

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching/ Equivalence	Measure of Hep C status Measure of depression / Anxiety	Results
			5.3% PWID in past 12 months 84.2% PWID>12months **Duration of injection drug use (years)**: [median(IQR)]: 7 (4-13) **Duration exposure to HCV (years)**: [median(IQR)]: 14.5 (4-24)			

Table A4.4: Studies comparing depression/anxiety in HCV-HIV co-infected versus HIV mono-infected (n=4)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching / equivalence**	**Measure of Hep C status** **Measure of Depression / Anxiety**	**Results**
Clifford et al. (2005) USA HIGH Route of HCV infection: Unknown	**30 HCV+/HIV+ co-infected patients** enrolled in a drug trial Mean age (SD): 40.27 (7.75) Male: 77%	**234 HIV-mono-infected patients** from same trial Mean age (SD): 38.05 (8.63) Male: 80%	**Exclusions:** Previous anti-retroviral or IFN treatment **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** Not reported **IV Drug use:** 47% - sample 4% - comparison **History of psychiatric or neurocognitive disorder:** Not reported **Co-infection (HBV):** 40% - sample 33% - comparison	**Matched on:** No matching **Imbalances between groups:** Age, gender, ethnicity, education, PWID **Adjusted for in analysis:** Authors say yes but no data reported	**HCV:** Anti-HCV antibodies **Depression/ Anxiety:** Centre for Epidemiologic Studies Depression Scale (CES-D) State-Trait Anxiety Inventory (STAI)	**Depression (CES-D)** Mean (SD) HCV+ patients: 18.77 (12.24) Comparison: 12.6 (10.34) *p*=0.006 **Anxiety (SAI)** Mean (SD) HCV+ patients: 51.37 (13.35) Comparison: 53.65 (12.42) *p*=0.368 **Clinically significant anxiety** HCV+ patients: 24/30 (80%) Comparison: 201/234 (86%) *p*= 0.406 Depressive symptomatology HCV+ patients: 17/30 (57%) Comparison: 74/234 (32%)

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching / equivalence**	**Measure of Hep C status** **Measure of Depression / Anxiety**	**Results**
						p= 0.013 Summary: HCV-HIV co-infected patients are more likely to be depressed than HIV-mono-infected controls; however there are no statistically significant differences between groups on measures of anxiety, clinically significant anxiety, or depressive symptomatology.
Thein et al. (2007) Australia HIGH Route of HCV infection: Mixed	**15 HCV+ pre-treatment patients recruited from tertiary level hepatitis clinic** for	**30 asymptomatic HIV-infected individuals from outpatient departments at major hospitals in Melbourne**	**Exclusions HCV group:** PWID Alcohol intake >100g/ week Cirrhosis Hepatocellular carcinoma Non-HCV chronic liver disease	**Matched on:** Age, gender, education **Imbalances between groups:** Age, gender, alcohol, PWID, exposure to HCV, liver	**HCV:** HCV-RNA HIV1-RNA **Depression/ Anxiety:** DASS	**Depression (DASS)** Mean (95% CI) HCV+HIV+ group: 7.87 (3.38-12.36) HIV+ only group: 8.77 (7.00-10.53) *p*=0.065 **Anxiety (DASS)**

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching / equivalence	Measure of Hep C status Measure of Depression / Anxiety	Results
	drug trial Mean age (SD): 35.5 (7.0) **Male:** 100%	Mean age (SD): 34.7 (7.4) **Male:** 100%	History neurological disorders Active infection CD4 count <200 **Exclusions HIV only group:** History current CNS infections Cryptococcal meningitis Toxoplasmosis Neurosyphilis Cerebral lymphoma Cytomegalovirus retinitis Pneumocystis carinii pneumonia Chronic drug or alcohol use History of seizures or	disease stage **Adjusted for in analysis:** Age and gender		Mean (95% CI) HCV+HIV+ group: 6.67 (3.24-10.10) HIV+ only group: 5.43 (4.61-6.25) *p*=0.564 Summary: Neither depression nor anxiety were significantly associated with HCV-HIV co-infected individuals, compared to an HIV-mono-infected group.

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching / equivalence	Measure of Hep C status Measure of Depression / Anxiety	Results
			major head injury **Acquisition:** Not reported **Liver disease status:** 66.7% no or minimal stage liver disease **Alcohol use:** 6.7% >= 5 alcoholic drinks past month **IV Drug use:** 53.3% PWID in past 12 months 33.3% PWID > 12 months **Duration injection drug use (years):** [median(IQR)]: 9 (3-10) **Duration exposure to HCV (years) [median(IQR)]:5 (2-7):** **Treatment status:** Pre-treatment			

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching / equivalence**	**Measure of Hep C status** **Measure of Depression / Anxiety**	**Results**
Von Giesen et al. (2004) Germany MODERATE Route of HCV infection: Mixed	**43 HCV- and HIV-positive cohort** followed at university hospital Dept. of Neurology, Gastro-enterology, Hepatology and Infectious Diseases Mean age (SD): 37.4 (7.8) **Male:** 65.1%	43 HIV-positive patients from same setting Mean age (SD): 38.0 (8.1) **Male:** 65.1%	**Exclusions:** HIV-associated dementia Primary CNS lymphoma CNS infections Cirrhosis Hepatic encephalopathy **Acquisition:** Homosexual/Bisexual: 9.3% - sample 9.3% - comparison PWID: 62.8% - sample 62.8% - comparison Blood product: 16.3% - sample 16.3% - comparison Heterosexual:	**Matched on:** No matching **Imbalances between groups:** Authors report no differences in age, ethnicity, gender, PWID, education but differences in tables look large **Adjusted for in analysis:** Not reported	**HCV:** HCV-RNA HIV1-RNA **Depression/ Anxiety:** Hamilton Depression Rating Scale (HDRS)	**Depression (HDRS)** Mean (SD) HCV+HIV+ group: 6.91 ± 5.69 HIV+ group: 6.86 ± 4.67 $p<0.0001$ Summary: Compared to patients with HIV only, patients co-infected with HIV and HCV are statistically significantly more likely to have higher depression score.

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching / equivalence	Measure of Hep C status Measure of Depression / Anxiety	Results
			11.6% - sample 11.6% - comparison Liver disease status: AST: 27 (36) - sample 32 (24) - comparison ALT: 34 (56) - sample 41 (38) - comparison **Alcohol use:** Not reported **Treatment status:** Untreated: 27.9% untreated-sample 41.9% - comparison HAART 41.9% - sample 20.9% - comparison			

Study **Country** **Risk of bias** **Relevance**	**Sample**	**Comparison**	**Nature of HCV infection**	**Matching / equivalence**	**Measure of Hep C status** **Measure of Depression / Anxiety**	**Results**
			Nucleoside analogues 30.2% - sample 37.2% - comparison **Co-infection:** All negative for HBV			
Yoon et al. 2011 USA MODERATE	**160 HCV- and HIV-positive patients attending one hospital clinic** at University of Washington Median age (for entire cohort): 45 years	**604 HIV-positive patients from same setting** Mean age (for entire cohort): 45 years Male: 88%	**Exclusions:** Patients currently receiving interferon therapy **Acquisition:** Not reported **Liver disease status:** Not reported **Alcohol use:** At-risk alcohol use **Drug use:** Any or current drug use **Treatment status:** ART status	**Matched on:** Not reported **Imbalances between groups:** Age Sex Ethnicity CD4 count ART status Current illicit drug use At-risk alcohol	**HCV:** Positive HCV antibody or RNA or genotype test **Depression/ Anxiety:** PHQ-9	**No depression (PHQ9: 0-4)** HCV+HIV group: 45/160 (28%) HIV+ only group: 245/604 (41%) **Mild depression (PHQ9: 5-9)** HCV+HIV group: 42/160 (26%) HIV+ only group: 166/604 (27%) **Moderate depression (PHQ9: 10-14)** HCV+HIV group: 31/160 (19%) HIV+ only group: 95/604 (9%)

Study Country Risk of bias Relevance	Sample	Comparison	Nature of HCV infection	Matching / equivalence	Measure of Hep C status Measure of Depression / Anxiety	Results
	Male: 83%			use BMI **Adjusted for in analysis:** Yes		**Moderately severe depression (PHQ9: 15-19)** HCV+HIV group: 26/160 (16%) HIV+ only group: 56/604 (9%) **Severe depression (PHQ9: 20-27**) HCV+HIV group: 16/160 (10%) HIV+ only group: 42/604 (7%) *p*=0.009

HCV and pain

Table A4.5: Arthralgia studies: key characteristics and findings (n = 7 studies)

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
Banks et al. (2007)	Cross-sectional	**54 HCV positive patients,** 32	**23 Nonalcoholic**	Chronic HCV	Questionnaire.	**Statistical tests:** x^2 test; logistic	**Having joint pain (% yes)** HCV+: 36/54 (66.6)

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
US MODERATE	study.	males, 22 females, mean age 45.7 ± 2.1 years, presenting to the outpatient Gastroenterology and Hepatology clinic between 3 Dec 2002, and 3 Apr 2003. Excluded when diagnosed HCV *and* NAFLD, HIV, or other liver disease causing joint pain, or receiving anti-virals / immuno-suppressants.	**Fatty Liver Disease (NAFLD) patients**, 13 females, 10 males, mean age 51.3 ± 5.0 years presenting to the outpatient Gastroenterology and Hepatology clinic between 3 December 2002 and 3 April 2003.	(diagnosis on new patient presentation or follow-up).	Presence of joint pain. Joint inflammatory complaints: morning stiffness lasting ≥ 1 hr daily or weekly symmetrical painful joint swelling improved by exercise.	regression. **Matched on:** Not reported. **Imbalances between groups:** BMI; alcoholism; smoking. **Adjusted for in analysis:** depression; use of pain relievers; alcohol use history; rheumatoid factor; ANA, cryoglobulin; diagnosis (HCV versus NAFLD); extent of fibrosis; Knodell score.	NAFLD: 15/23 (65.2) p = 0.90 **Reported joint inflammatory complaints (% yes)** HCV+: 13/54 (36.1) NAFLD: 6 /23 (40.0) p = 0.79 In logistic regression analysis, we could not determine a variable that significantly predicted the presence of joint pain. This included demographic information, the presence of RF, antinuclear antibodies, and diagnosis. We also looked at the association between the amount of histologic liver inflammation and the presence of joint pain.

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
Calore et al. (2012) U.S. HIGH	Cross-sectional study.	**381 of 408 veterans undergoing total joint arthroplasty** between August 2007 and May 2009, 94% male, mean age 64 years (range 43-92 years).	**General veteran population** (Sloan et al. 2004).	Anti-HCV antibodies and HCV RNA.	Patients undergoing total joint arthroplasty.	**Statistical tests:** Not reported. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	32/381 (8.4%) Anti-HCV positive. 17/381 (4.5%) viraemic. Seroprevalence of HCV infection of users of the Veterans Affairs (VA) medical system (5.4%).
De Vita et al. (2002) Italy HIGH	Cross-sectional study.	**62 consecutive Sjoegren's Syndrome (SS) patients**.	**12 HCV+, 50 HCV-** HCV+ patients: 11 females, 1 male, mean age 69 ± 9.1 HCV- patients: 46 females, 4 males, mean age 56 ± 13.4	Anti-HCV antibodies and HCV RNA.	'Clinical evaluation'	**Statistical tests:** x^2 test (with Yates correction) **Matched on:** Not reported. **Imbalances between groups:** Age **Adjusted for in analysis:** Not reported.	10/12 (83%) HCV positive SS patients with arthralgia/ arthritis 36/50 (72%) HCV negative SS patients with arthralgia/ arthritis P = not significant

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
Rieu et al. 2002 France HIGH	Cross-sectional study.	**49 patients**, 18 men, 31 women, mean age 59.96 ± 12 years with clinical manifestations attributable to cryoglobulinaemia seen between 1978 and 1998 in an internal medicine department.	**33 HCV+** **14 HCV-**	Anti-HCV antibodies and HCV RNA.	Not reported.	**Statistical tests:** x^2 test **Matched on:** -Not reported. **Imbalances between groups:** Transaminases were significantly higher in HCV+ patients (57.6% vs 14.3%, p < 0.05). **Adjusted for in analysis:** Not reported.	HCV positive patients with arthralgias 20/33 (60.6%) HCV negative patients with arthralgias 3/14 (21.4%) P = 0.025
Rivera et al. (1997) Spain HIGH	Case-control study and cross-sectional study.	**112 consecutive out-patient rheumatology clinic FS patients**, 3 males, 109 females, mean age 51.43 ± 11.08 (25-78	**112 age and sex-matched rheumatoid arthritis (RA) patients**, 3 males, 109 females, mean age 51.28 ±11.20 (24-76	Anti-HCV antibodies, confirmatory RIBA and HCV RNA.	Physical examination.	**Statistical tests:** x^2 test; Fisher's exact test **Matched on:** age; sex **Imbalances between groups:** Not reported. **Adjusted for in**	**Diffuse arthralgias:** Chronic HCV positive patients: 31/58 **General surgery controls:** 13/58 P< 0.001 (95% CI 12.5-49.4)

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
		yrs). Those with systemic, inflammatory rheumatic diseases, HIV and HBV excluded. 58 chronic HCV hospital hepatology unit patients, 32 males, 26 female, mean age 46.22 ± 12.88 (22-70yrs).	yrs). All patients with ACR diagnostic criteria. 58 age and sex-matched patients attending hospital general surgery unit.			**analysis:** Not reported.	
Tsui et al. (2012) US MODERATE	Prospective cohort study.	**200 HIV patients with alcohol problems and co-infected with HCV**, mean age 44 ± 7 years, 54	**197 HIV patients with alcohol problems but uninfected with HCV**, mean age 41 ±	Anti-HCV antibodies and HCV RNA.	Symptoms measured using the HIV Symptom Index (Justice, et al., 2001), a	**Statistical tests:** GEE logistic regression models. **Matched on:** No matching. **Imbalances**	**Muscle or joint pain** HIV mono-infected patients: 129/197 (66%) HCV + HIV patients: 153/200 (77%) p = 0.02

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
		(27%) female. Recruitment from a previous cohort study: an intake clinic for HIV-infected patients, HIV primary care and speciality clinics at two hospitals, homeless shelters, drug treatment programmes, subject referrals, and flyers from August 2001 to July 2003.	8 years, 46 (23%) female.		validated 20-question inventory of symptoms common in the setting of HIV infection. Headache, muscle/joint pain, and peripheral neuropathy were defined as a response other than 'I do not have this symptom'.	**between groups:** HCV + participants more likely to be older, homeless, recently used injection drugs, diabetic, and have substantial depressive symptoms. **Adjusted for in analysis:** Time; Age; sex; black race; marital status; homeless; smoking; alcohol use; drug use; low CD4 count; HIV viral load and HIV medication.	**Final model: muscle or joint pain** OR 1.45, CI 95% 1.06 – 1.97, p = 0.02 **Final model + depressive symptoms: muscle or joint pain** OR 1.33, CI 95% 0.98 – 1.81, p = 0.07
Yucel et al. (2005)	Cross-sectional	**284 of 344 end-stage renal disease patients**	**Association between Hep C status and**	Anti-HCV antibodies and HCV	Self-reporting via questionnair	**Statistical tests:** Backward logistic	Anti-HCV positivity correlated with arthralgia

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure of arthralgia	Matching/ equivalence/ adjustment	Results
Turkey HIGH	study.	**receiving chronic haemodialysis therapy** (206 males, 138 females), with a mean dialysis duration of 4.4 years, and mean age 44.4 ± 16.0 years.	**arthralgia determined**.	RNA.	e and patient history via medical records.	regression. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Gender; age; dialysis duration; cause of renal failure; HBV; HCV	p<0.001.

Table A4.6: Arthritis studies: Key characteristics and findings (n = 11 studies)

Study **Country** **Risk of bias**	**Design**	**Sample**	**Comparison(s)**	**Measure of Hepatitis C status**	**Measure/ diagnosis of arthritis**	**Matching/ equivalence/ adjustment**	**Results**
Baffoni et al. (1993) Italy HIGH	Case-control study.	**100 rheumatoid arthritis (RA) patients**. History of hepatitis, transfusion, IV drug use and haemodialysis, present or past raised values of serum AST and ALT were excluded.	**50 control subjects with rheumatoid factor (RF); Italian blood donors**.	Anti-HCV antibodies with confirmatory recombinant immunoblot assay (RIBA) test.	Revised 1987 Criteria of the American Rheumatism Association.	**Statistical tests:** Not reported. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	6/100 (6%) RA patients = HCV+ 8/50 (16%) controls with RF = HCV+ 0.95% Italian blood donors = HCV+
Borque et al. (1991) Spain HIGH	Case-control study.	**36 rheumatoid arthritis patients** with rheumatoid factor (RF) values	**40 RF negative carriers of chronic broncho-pneumonia** with normal serum immunoglobulin values.	Anti-HCV antibodies.	Revised 1987 Criteria of the American Rheumatism Association.	**Statistical tests:** Not reported. **Matched on:** Not reported. **Imbalances between**	12/36 (33%) RA patients = HCV+ 0/40 (0%) chronic broncho-pneumonia patients = HCV+ 1.2% healthy controls =

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
		between 25 and >3750 UI/mL				**groups:** Not reported. **Adjusted for in analysis:** Not reported.	HCV+
Congia et al. (1996) Italy HIGH	Cross-sectional study.	**420 patients with thalassemia major** (228 males). HIV+ patients excluded.	**314 HCV+** **106 HCV-**	Anti-HCV antibodies and/or HCV RNA.	Not reported.	**Statistical tests:** x^2 test; Fisher's exact test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**Arthritis:** 16/314 (5%) HCV+ patients 0/106 (0%) HCV- patients P < 0.008
D'Amico et al. (1996) Italy	Case-control study.	**49 consecutive patients** (hospitalised	**83 consecutive patients with osteoarthritis** coming from the	Anti-HCV antibodies with confirmatory	American Rheumatism Association (ARA) criteria.	**Statistical tests:** Fisher's exact test **Matched on:**	RA patients = 7/49 (14.2%) HCV+ OA patients = 1/83 (1.2%) HCV-

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
HIGH		or outpatient) with RA, 7 males, 42 females, mean age 61 (range 18-81 years)	same geographic region, 12 males, 71 females, mean age 59 (range 20-97 years)	RIBA test.		Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	P < 0.005
De Vita et al. (2002) Italy HIGH	Cross-sectional study	**62 consecutive Sjoegren's Syndrome patients**	**12 HCV+** **50 HCV-** HCV+ patients, 11 females, 1 male, mean age 69 ± 9.1 HCV- patients, 46 females, 4 males, mean age 56 ± 13.4	Anti-HCV antibodies with confirmatory RIBA test and HCV RNA.	'Clinical evaluation'	**Statistical tests:** x^2 test (with Yates correction) **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	HCV RNA was amplified in the serum of 10/11 cases (data not available for the remaining patient). **Arthralgia/arthritis:** 10/12 (83%) HCV+ patients 36/50 (72%) HCV – patients P = Not significant

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
Gharagozloo et al. (2001) Iran HIGH	Case-control study	**30 chronic RA patients**	**42 Essential Mixed Cryoglobulinaemia (EMC) patients;** **45 Multiple Myeloma (MM) patients;** **23 B-cell chronic lymphocytic leukaemia (B-CLL) patients**	Anti-HCV antibodies with confirmatory RIBA test.	Not reported.	**Statistical tests:** x^2 test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**EMC:** HCV+ ELISA 29/42 (69%) HCV+ RIBA 29/42 (69%) **MM:** HCV+ ELISA 8/45 (18%) HCV+ RIBA 5/45 (11%) $p < 0.06$ **B-CLL:** HCV+ ELISA 2/23 (8.7%) HCV+ RIBA 1/23 (4.3%) **RA:** HCV+ ELISA 1/30 (3.3%) HCV+ RIBA 0/30 (0%)
Guennoc et al. (2009) France HIGH	Case-control study.	**808 of 813 recent-onset arthritis patients** from the French Society for Rheumatology ESPOIR	**French general population** (Dubois et al. 1997).	Anti-HCV antibodies with confirmatory RIBA test.	Patients with definite or probable clinical diagnosis of rheumatoid arthritis or a diagnosis of	**Statistical tests:** Not reported. **Matched on:** Not reported. **Imbalances between groups:** Not	HCV+: ESPOIR cohort anti-HCV+: 16/808 (1.98%) ESPOIR cohort RIBA+: 7/808 (0.86% 95% CI 0.38%-1.86%) French general population anti-HCV

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
		cohort, 189 males, 624 females, mean age 48 ± 12.5 years.			undifferentiated arthritis with a potential for progressing to RA 1987 ACR criteria. There was 'no particular definition' of probable or undifferentiated RA.	reported. **Adjusted for in analysis:** Not reported.	RIBA+ (Dubois et al. 1997): 72/6,283 (1.15%); weight prevalence 1.05, 95% CI: 0.75-1.34.
Hsu et al. (2003) US MODERATE	Cross-sectional study employing data from NHANES III conducted between 1988 and 1994.	**6,596 people ≥60 years** sampled via stratified, multistage probability method. Final sample = 4,769 (those with HCV/RA status	**Relative odds of RA in relation to HCV serology and covariates determined for those ≥60 years.**	Anti-HCV antibodies and HCV RNA.	Probable RA = 3 of 6 revised 1987 American College of Rheumatology (ACR) criteria. Possible RA = 2 of 6 ACR criteria.	**Statistical tests:** Design-based logistic regression **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for**	Probable RA: HCV+ = 2/196. Possible RA: HCV+ = 5/313. No RA: HCV+ = 58/4,456. Probable RA : HCV RNA+ = 1/196. Possible RA : HCV RNA+ = 3/313. No RA: HCV RNA+ = 32/4456.

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
		determined).				**in analysis:** age; gender; ethnicity.	Probable RA: OR HCV Ab+: 0.40, 95% CI: 0.06-2.60, p=0.33 Adjusted OR HCV Ab+: 0.44, 95% CI: 0.07-2.80) p=0.37 Adjusted OR HCV RNA+: 0.77, 95% CI: 0.10-6.19. Possible RA: OR HCV Ab+: 0.62, 95% CI: 0.19-1.99, p=0.41 Adjusted OR HCV Ab+: 0.66, 95% CI: 0.20-2.15, p=0.48 Adjusted OR HCV RNA+: 0.90, 95% CI: 0.20-4.12. Subjects with probable RA had similar proportions with HCV Ab+ (p=0.32) and RNA+ (p=0.77) to those without RA, as did those

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
							with possible RA (Ab+ p=0.41, RNA+ p=0.92).
Maillefert et al. (2002) France HIGH	Case-control study.	**309 rheumatoid arthritis patients admitted to hospital** in two rheumatology departments (232 women, 77 men, mean age (SD) 54.1 (14.8) years.	**French general population** (Dubois et al. 1997).	Anti-HCV antibodies and HCV RNA.	ACR criteria for RA.	**Statistical tests:** Not reported. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	HCV+ serology in two patients (0.65%; 95% CI: 0.08-2.3%). HCV RNA+ in the first patient (previously diagnosed), negative in the second (0.32%; 95% CI 0.008% to 1.8 %, exact binomial method). 0.85% prevalence of past or active, and a 0.42% prevalence of active HCV infection in patients with RA. French general population anti-HCV RIBA+ (Dubois et al. 1997): 72/6,283 (1.15%); weight prevalence 1.05, 95% CI: 0.75-1.34.

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hepatitis C status	Measure/ diagnosis of arthritis	Matching/ equivalence/ adjustment	Results
Rivera et al. (1999) Spain HIGH	Case-control study.	**303 patients with RA**, 236 females and 67 males, mean age 58.3 ± 13.0 years (range 22-89).	**315 first-time blood donors**, 211 men, 104 women, mean age 33.4 ± 11.7 years.	Anti-HCV antibodies, confirmatory RIBA and HCV RNA.	Revised 1987 Criteria of the American Rheumatism Association.	**Statistical tests:** x^2 test; Fisher's exact test **Matched on:** Not reported. **Imbalances between groups:** age; sex **Adjusted for in analysis:** Not reported.	**RA patients:** Anti- HCV+ 23/303 (7.6%) RIBA+ 13/303 (4.3%) RNA+ 7/303 (2.3%) **Blood donor controls**: HCV+ (antibodies) 3/315 (0.95%, 95% CI: 0.03-0.10, p<0.001) Proportion RIBA + among ELISA+ not significantly different between RA patients and blood donors. RA patients: 13 RIBA+, 3 indeterminate, 3 negative, missing data for 3 patients. Blood donors (38 HCV+ donors): 27 RIBA+, 5 indeterminate, 6 negative.

Study **Country** **Risk of bias**	**Design**	**Sample**	**Comparison(s)**	**Measure of Hepatitis C status**	**Measure/ diagnosis of arthritis**	**Matching/ equivalence/ adjustment**	**Results**
Yucel et al. (2005) Turkey HIGH	Cross-sectional study.	**284 of 344 end-stage renal disease patients** receiving chronic haemodialysis therapy (206 males, 138 females), with a mean dialysis duration of 4.4 years, and mean age 44.4 ± 16.0 years.	**Association between Hep C status and arthritis determined.**	Anti-HCV antibodies and HCV RNA.	Self-reporting via questionnaire and patient history via medical records.	**Statistical tests:** Backward logistic regression. **Matched on:** Not reported. **Imbalances between groups:** Not reported. Adjusted for: gender; age; dialysis duration; cause renal failure; HBV, HCV.	Anti-HCV positivity correlated with arthritis $p<0.001$.

Table A4.7: Fibromyalgia syndrome (FS) studies: key characteristics and findings (n = 9 studies).

Study Country Risk of bias	**Design**	**Sample**	**Comparison(s)**	**Measure of Hep C status**	**Measure/ Diagnosis of Fibromyalgia (FS)**	**Matching/ Equivalence/ Adjustment**	**Results**
Buskila et al. (1997) Israel MODERATE	Cross-sectional study.	**90 consecutive, unselected HCV+ liver clinic patients**, 48 males, 42 females, mean age 57 (SD 15): 8 patients no chronic liver disease; 41 (11 female) patients chronic hepatitis; 41 (28 female) patients with cirrhosis. No interferon therapy during the study.	**Control Group 1: 128 healthy hospital personnel** without evidence of HCV infection or any liver enzyme abnormalities, 70 males, 58 females, mean age 48 (SD 10). **Control Group 2: 32 patients (17 female) with non-HCV related cirrhosis**.	Anti-HCV antibodies and HCV RNA.	1990 Criteria of the American College of Rheumatology (ACR): widespread pain in combination with tenderness at 11 or more of 18 specific tender points.	**Statistical tests:** x^2 test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**Prevalence of FS by HCV disease severity:** No chronic liver disease: 0/8 (-) Chronic hepatitis: 4/41 (9.8%) Cirrhosis: 10/41 (24.4%) $p < 0.08$ **Prevalence of FS in HCV patients 14/90 (15.5%) versus healthy controls:** 0/128 (0%), $p < 0.001$. **Prevalence of FS in HCV patients 14/90 (15.5%) versus patients with non-HCV related cirrhosis:** 1/32 (3.1%), $P < 0.01$.

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
De Vita et al. (2002) Italy HIGH	Cross-sectional	**62 consecutive Sjoegren's Syndrome patients**	**12 HCV+** **50 HCV-** HCV+ patients, 11 females, 1 male, mean age 69 ± 9.1 HCV- patients, 46 females, 4 males, mean age 56 ± 13.4	Anti-HCV antibodies and HCV RNA.	'Clinical evaluation'	**Statistical tests:** x^2 test (with Yates correction) **Matched on:** Not reported. **Imbalances between groups:** age; liver disease; lung disease. **Adjusted for in analysis:** Not reported.	**Fibromyalgia syndrome:** HCV+ patients = 4/12 (33%) HCV- patients = 7/50 (14%) P = not significant
Goulding et al. 2001 Ireland HIGH	Cross-sectional	**77 HCV+ patients attending a hepatology clinic**. 49 women infected via contaminated anti-D immunoglobulin, 25 women	**25 age and sex-matched healthy volunteers**. **General population** (Wolfe et al. 1995).	Anti-HCV antibodies and HCV RNA.	ACR criteria.	**Statistical tests:** t-test **Matched on:** age; sex **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**Fibromyalgia syndrome:** HCV+ patients = 4/77 (5%) Anti-D infected = 4/49 (8.2%) IDVU = 0/25 (0%) General population = 2% (Wolfe et al. 1995). **Mean number of**

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
		infected by IV drug use, 3 women infected by transfusion; mean age 48 ± 7.19, 23 (47%) PCR+, mean duration of infection 21 years. 25 PWID, 15 male, 10 female, mean age 27.6 ± 6.29, 71% PCR+, mean duration infection 10yrs.					**tender points:** Anti-D infected = 5.0 Controls = 2.8 p = 0.03 PWID = 2.48 P < 0.01 There was no statistically significant difference in the number of tender points between PCR positive and negative patients.
Kandemir et al. 2006 Turkey HIGH	Cross-sectional study.	**40 consecutive anti-HCV positive patients**. All patients were newly diagnosed	**40 healthy controls**. **40 consecutive FM patients**	Anti-HCV antibodies and HCV RNA	Severity of pain: visual analogue scale 0-10 points with 10 denoting	**Statistical tests:** One-way analysis of variance. **Matched on:** Not reported.	**Mean number of tender points:** 14.5 ± 0 for FM patients 4.9 ± 4.9 for HCV

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
		and none received interferon therapy at enrolment. All patients and control subjects were female.	(age and sex matched). Patients with systemic, inflammatory or rheumatic diseases were excluded. Patients randomly recruited without any evidence of HCV infection/ liver enzyme abnormalities.		the worst possible condition. Manual pressure applied over tender point by thumb palpitation was 4 kg/cm^2.	**Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	patients 3.3 ± 4.7 for healthy controls p= 0.01 **Mean Visual Analog Score:** 6.05 ± 2.2 cm for FM patients 4.0 ± 2.1 cm for HCV patients 4.5 ± 2.3 cm for healthy controls p= 0.00
Kozanoglu et al. (2003) Turkey HIGH	Cross-sectional study.	**95 consecutive HCV+ patients**, 33 male, 62 female, mean age 45.8 ± 9.6 (18–65).	**95 healthy hospital staff** with no chronic disease history, 36 male, 59	Anti-HCV antibodies and HCV RNA.	Presence of widespread pain ≥ 3 months and tenderness in at least 11 of 18 specific	**Statistical tests:** Fisher's exact test **Matched on:** Not reported. **Imbalances between groups:** Not reported.	**Fibromyalgia syndrome:** 18/95 (18.9%) HCV+ 5/95 (5.3%) healthy controls p = 0.007

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
		None of the patients had received interferon treatment in the 6 months before the study.	female, mean age 43.1 ± 10.9 (19–65).		anatomic sites, based on the 1990 ACR criteria.	**Adjusted for in analysis:** Not reported.	
Mohammad et al. (2012) Ireland MODERATE	Cross-sectional study.	**185 consecutive HCV+ patients of a hepatology clinic** Dublin: no decompensated or autoimmune liver disease, arthritis, vasculitis, HBV, HDV or HIV, end-stage renal failure, organ transplantation, cancer, methadone or	**FS status, demographic and viral characteristics were determined.**	Anti-HCV antibodies and HCV RNA.	1990 ACR criteria.	**Statistical tests:** univariate logistic regression analysis. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	Female sex, ≥ 45 years age, history of depression, acquisition of HCV through blood transfusion and infection with HCV genotype 1 were independently associated with presence of FS. **Blood transfusion acquired HCV:** FS+ patients: 65/106 FS – patients: 35/79 p = 0.001

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
		interferon use in the past 6 months. 75 males, 110 females, mean age 48.7 (21-81).					HCV genotype 1: FS+ patients: 81/106 FS- patients: 52/79 p = 0.001 No association between FS and viral load (p = 0.174).
Narvaez et al. (2005) Spain HIGH	Case-control study.	**115 fibromyalgia patients enrolled 1996-2003 without any disease** (other than HCV infection) that might explain the presence of fibromyalgia, 10 males, 105 females, mean age 45 ± 10.	**Comparative study was performed on the total general population and on different age groups** (aged 25-44 and 45-65 yrs).	Anti-HCV antibodies, confirmatory RIBA and HCV RNA.	1990 ACR criteria.	**Statistical tests:** x^2 test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**HCV infection:** 22-44 yrs: FS patients 1/45 (2.22%) General population 1.74% (1.62-1.86) p = NS 45-64 yrs: FS patients 2/70 (2.85%) General population 2.54% (2.37-2.71) p = NS

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
							Total: FS patients 3/115 (2.6%) General population 2.5% (1.8-3.2)/ 2.64% (2.53-2.75) p = NS
Palazzi et al. (2008) Italy MODERATE	Case-control study.	**152 consecutive FS patients seen in the outpatient clinic of the rheumatology division** of Villa Pina Clinic, Chieti, Italy, 149 females, 3 males, mean age 54 ± 11.9 (21-83).	**Statistically comparable group of patients suffering from osteoarthritis or sciatica due to a herniated disc**, 149 females, 3 males, mean age 55.3 ± 12.5 (20-82).	Anti-HCV antibodies, confirmatory RIBA and HCV RNA.	1990 ACR criteria.	**Statistical tests:** Fisher's exact test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	**HCV+:** FS patients 7/152 (4.6%) Controls 5/152 (3.3%) P = 0.77. **HCV RNA +:** 6/152 (3.9%) FM patients 4/149 (2.7%) controls
Rivera et al. (1997)	Case-control	**112 consecutive**	**112 age and sex-matched**	Anti-HCV antibodies,	1990 ACR criteria.	**Statistical tests:** x^2 test; Fisher's exact	**HCV infection:** Anti-HCV+ FS patients:

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure/ Diagnosis of Fibromyalgia (FS)	Matching/ Equivalence/ Adjustment	Results
Spain HIGH	study and cross-sectional study.	**rheumatology clinic FS out-patients**, 3 males, 109 females, mean age 51.43 ± 11.08 (25-78). Patients with systemic/ inflammatory rheumatic diseases and HIV/HBV excluded. 58 chronic HCV hospital patients, 32 males, 26 female, mean age 46.22 ± 12.88 (22-70 yrs)	**rheumatoid arthritis (RA) patients**, 3 males, 109 females, mean age 51.28 ±11.20 (24-76 yrs). All RA patients Satisfied ACR diagnostic criteria. **58 age and sex-matched patients attending hospital general surgery unit**.	confirmatory RIBA and HCV RNA.		test **Matched on:** age; sex **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	17/112 (15.2%) RIBA+FS patients: 16/112 (14.3%) HCV RNA+ FS patients: 13/112 (11.6%) RA patients: 6/112 (5.3%) RA vs FS (HCV+) p<0.05 (95% CI 1.9-17.6) RA vs FS (RIBA+) p = NS RA vs FS (HCV RNA+) p < 0.01 (95% CI 2.5-17.13). **Fibromyalgia:** Chronic HCV+ patients: 6/58 (5 female) General surgery controls: 1/58 (female) RR 6.0 (P < 0.05 95% CI -1.6-18.8) [sic]

Table A4.8: Disparate pain outcomes: Key characteristics and findings (n = 3 studies)

Study **Country** **Risk of bias**	**Design**	**Sample**	**Comparison(s)**	**Measure of Hep C status**	**Measure of Arthralgia**	**Matched variables**	**Results**
Barkhuizen et al. (1999) US HIGH	Cross-sectional study.	**121 HCV positive hepatology clinic patients**	**118 HCV negative hepatology clinic patients**	Patients who were positive for anti-HCV antibodies with second generation ELISA test assumed to have current active HCV infection.	Questionnaire relating to muscle, joint, back and neck pain, and joint swelling. Patients indicated distribution of pain on a body diagram. Pain diagrams scored by a rheumatologist blinded to hepatic diagnosis and HCV status.	**Statistical tests:** one-way ANOVA; Mantel-Haenszel X^2 test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	No statistically significant association between HCV positivity and back, neck, axial or diffuse pain. **HCV+ versus HCV- chronic liver disease patients:** Any musculoskeletal (MSS) pain OR 3.3, 95% CI: 1.9-6.3, p = 0.0001 Morning stiffness OR 3.2, 95% CI: 1.8-5.6, p < 0.0001 Joint pain OR 3.4, 95% CI: 1.9-6.0, p <0.0001 Muscle pain OR 2.6, 95% CI: 1.5-4.6, p = 0.0009 Pain all over OR 3.3, 95CI: 1.7-7.0, p < 0.001 MSS pain more frequent among those with isolated HCV infection

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure of Arthralgia	Matched variables	Results
							than isolated HBV or alcoholic liver disease patients (91%, 59% and 48% respectively, p = 0.004). The addition of alcoholic liver disease or HBV to HCV did not appear to increase the likelihood of MSS pain. No statistically significant association between MSS pain and liver disease severity in a subset of 90 HCV positive patients with liver biopsies available. MSS pain present in 87% of 69 severe liver disease patients versus 67% of 21 mild-to-moderate disease patients (p > 0.05). MSS pain was present in 64% of 47 cirrhosis patients versus 46% of 43 patients without cirrhosis (p > 0.05) No statistically significant

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure of Arthralgia	Matched variables	Results
							association between MSS pain and route of infection in a subset of 110 HCV positive patients.
Isaacs et al. (2013) UK HIGH	Cross-sectional study.	**118 HCV patients at the Digestive Diseases Unit of the Brighton and Sussex University Hospital Trust** not co-infected with HIV or HBV, but with completed standard antiviral treatment (pegylated interferon-α and ribavirin).	**Those with and without sustained viral clearance** (SVR).	Unreported.	Chronic widespread pain (CWP) according to the Manchester criteria (pain in the axial skeleton and at least two contralateral body quadrants for at least 3 months).	**Statistical tests:** X^2 test **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Not reported.	Significant positive associations between SVR and changes in CWP RR 6.0, 95% CI 0.75 – 48.29 (p = 0.038).

Study Country Risk of bias	Design	Sample	Comparison(s)	Measure of Hep C status	Measure of Arthralgia	Matched variables	Results
Morasco et al. (2010) US MODERATE	Cross-sectional study.	**49 HCV positive patients** (a subset from a larger study (Huckans et al. 2009) with medical record of a detectable HCV viral load completing all measures of interest.	**Correlation between viral load and pain intensity investigated**.	Quantitative PCR tests were used as an indicator of viral load.	Pain intensity was assessed with a 0–10 numeric rating scale (NRS), where 0 = 'no pain' and 10 = 'extremely severe pain'.	**Statistical tests:** Hierarchical multiple regression analyses. **Matched on:** Not reported. **Imbalances between groups:** Not reported. **Adjusted for in analysis:** Step 1: age; BMI Step 2: viral load; liver disease severity; prescribed opioid Step 3: severity of depression; substance dependence severity.	Non-significant correlation between HCV viral load and pain intensity −0.170, $p > 0.05$. In the regression model predicting pain intensity, only the model with psychosocial variables included was significant. The only independent predictor of pain intensity was depression severity.

Table A4.9: Association between HCV status and pain or painful conditions: liver disease status of patients in included studies (n = 26 studies)

Study	Severity of liver disease
Baffoni et al. (1993)	Patients and control subjects with present or past raised values of serum AST and ALT were not included.
Banks et al. (2007)	All patients had laboratory evidence of transamminitis at some point during the 6 months prior to their entry into the study. Patients with liver biopsy proven NAFLD or chronic HCV were included. Liver histology results from biopsy of each subject, including amount of fibrosis and Knodell score, was used as an indicator of the severity of liver disease (amount of hepatic inflammation seen).
Barkhuizen et al. (1999)	Patients' hepatic diagnoses derived by the hepatology consultant were recorded. More than one diagnosis was allowed because of the frequent co-occurrence of diseases such as HCV and alcoholism. The most recent laboratory evaluation of liver function tests including bilirubin, AST, ALT, ALP and albumin were noted.
Borque et al. (1991)	Not reported.
Buskila et al. (1997)	Patients were divided into 3 groups: group A, anti-HCV positive with normal ALT levels and no signs of chronic liver disease; group B, chronic liver disease confirmed by liver biopsy; and group C, patients with cirrhosis (diagnosis confirmed by a liver biopsy or the presence of portal hypertension). No patient received interferon therapy during the study. Two control groups were used: healthy controls and patients with non-HCV related cirrhosis (caused by hepatitis B or autoimmune hepatitis).
Calore et al. (2012)	Not reported.
Congia et al. (1996)	Chronic hepatitis was diagnosed by the histological findings of minimal to severe hepatocellular necro-inflammation and fibrosis in liver biopsy specimens. Patients were characterised pathologically by minimal to severe chronic hepatitis with mild to severe fibrosis without any notable differences in histological severity between the HCV positive and negative cases.
D'Amico et al. (1996)	Each patient was considered as having chronic hepatitis if ALT tested above the normal level for at least a 6 month period.

Study	Severity of liver disease
De Vita et al. (2002)	Not reported.
Gharagozloo et al. (2001)	Not reported.
Goulding et al. (2001)	Those who were PCR positive underwent liver biopsy. Liver histology in the patients with fibromyalgia: the PCR-negative patient had a normal liver biopsy; two of three PCR-positive patients had mild histological changes, and the third had moderate changes i.e. bridging fibrosis.
Guennoc et al. (2009)	HCV positive patients had significantly higher serum ALT levels (41.5 IU versus 23.2 IU, p = 0.02) and AST levels (39.2 IU versus 21.83 IU, p = 0.001) compared with the overall population. However, only 2 HCV positive patients had AST or ALT levels > 40 IU (normal limit for aminotransferases < 40).
Hsu et al. (2003)	Not reported.
Isaacs et al. (2013)	Not reported.
Kandemir et al. (2006)	The mean AST and ALT levels were 66.2± 70.2 and 51.8 ± 53.4 in HCV patients.
Kozanoglu et al. (2003)	All had chronic hepatitis confirmed by liver biopsy. None of the patients had received interferon treatment in the 6 months before the study. Laboratory values for prothrombin time, AST, ALT, ALP and total protein were significantly higher in the HCV group than in the control group ($p < 0.05$). Albumin levels were significantly lower in the HCV group ($p < 0.001$). Platelet count and levels of glucose were not different between the groups ($p > 0.05$).
Maillefert et al. (2002)	Serum aminotransaminases, gamma-glutamyl aminotransferase and ALP were increased in 4%, 14% and 4% of patients respectively, most of the increased transaminases being due to therapy. Serum aminotransaminases and ALP were in the normal range in two HCV positive patients whereas serum gamma-glutamyl aminotransferase was increased twofold in one and was in the normal range in the other.
Mohammad et al. (2012)	Individuals with decompensated liver disease, concomitant autoimmune liver disease, arthritis, vasculitis, co-infection with hepatitis B or D or HIV, end-stage renal failure, organ

Study	Severity of liver disease
	transplantation, cancer, receiving methadone, or receiving interferon therapy in the past 6 months were excluded.
Morasco et al. (2010)	The APRI was used as the measure of liver disease severity; this is a non-invasive index that reliably predicts fibrosis and cirrhosis in HCV patients using routine laboratory data, with higher scores indicating more advanced liver disease. The calculation for APRI = (AST level/upper limit of normal)/(platelet counts x [10^9/litres]) x 100.
Narvaez et al. (2005)	HCV infection manifested itself by extrahepatic symptoms with clinically minimal liver disease (normal or mildly elevated serum transaminases on serial laboratory evaluation) and with no cirrhotic complications.
Palazzi et al. (2008)	Transaminases were high in three out of seven FM patients and three out of five controls.
Rieu et al. (2002)	Transaminases were significantly higher in the HCV positive patients than in the HCV negative patients (57.6% versus 14.3%, $p < 0.05$).
Rivera et al. (1999)	The presence of HCV RNA was detected in 7 (2.3%) patients, all with ALT elevation at the time of the study. The ALT mean value in these patients was 71.2 ± 30.6 U/l (range 54–165). Among these patients, one was taking methotrexate and another azathioprine at the time of the study. A retrospective analysis showed that previous ALT determinations were always altered in these 7 rheumatoid arthritis patients, and no correlations were found between the potential hepatotoxic drugs taken and the ALT levels.
Tsui et al. (2012)	Not reported.
Yucel et al. (2005)	Not reported.

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase

Table A4.10: Arthralgia: studies at high risk of bias (n = 4)

Calore et al. (2012) examined a population of US veterans undergoing total joint arthroplasty which they found 'roughly corresponds to the Vietnam era veteran population that is known to have the highest prevalence of hepatitis C in the VA system' (mean age 64, range 43-92 years). The prevalence of hepatitis C in this population was compared to that of the US general population and general veteran population (both of whom are likely to have different risk profiles from the population examined). However, the principal aim of this study appeared to be to assess risk of HCV infection in operating surgeons due to sharps injuries.
De Vita et al. (2002) compared the presence of arthralgia/arthritis in a very small sample of HCV positive (n = 12) compared to HCV negative (n = 50) Sjoegren's Syndrome patients in Italy. Significant differences ($P < 0.05$) were observed in mean age (69 versus 56 years) and presence of liver disease (50% versus 2%), rendering comparison between the two groups unsafe.
Rieu et al. (2002) examined the presence of arthralgia in a very small sample of HCV positive (n = 33) compared to HCV negative (n = 14) symptomatic cryoglobulinaemia patients in France. The sociodemographic characteristics of the HCV positive and negative patients were not provided and therefore we were unable to judge if these groups are comparable. In addition, transaminases were significantly higher in the HCV positive patients than in the HCV negative patients (57.6% versus 14.3%, $p < 0.05$) indicating a disparity between groups in terms of liver disease.
Rivera et al. (1997) described a cross-sectional study in which they compared the prevalence of diffuse arthralgias in 58 HCV chronic hepatitis hospital hepatology unit patients versus 58 age and sex-matched patients attending a hospital general surgery unit. Sociodemographic characteristics other than age and gender were not described for either group, so we were unable to judge if they were comparable.
Yucel et al. (2005) performed a backward logistic regression analysis incorporating gender, age, duration of dialysis, cause of renal failure, hepatitis B infection, HCV infection and various laboratory parameters to determine the association between these factors and the prevalence of arthralgia in 284 of 344 chronic haemodialysis patients (32% anti-HCV-positive). They found 'a correlation' between arthralgia and anti-HCV positivity ($p < 0.001$). It should be noted however, that smoking, socio-economic status and liver disease severity were *not* considered in their analysis and as a result we cannot place a great deal of confidence in these findings. Furthermore, since the results are presented with respect to anti-HCV positivity, the study should be thought of as examining the relationship between past and/or active infection rather than chronic infection. In addition, the sample in this study was composed entirely of patients with end stage renal disease, thus limiting generalisability to other populations.

Table A4.11: Arthritis: studies at high risk of bias (n = 10)

Baffoni et al. (1993) conducted a case-control study comparing anti-HCV positivity in 100 rheumatoid arthritis (RA) patients with 50 healthy, rheumatoid factor (RF) positive controls as well as a population of Italian blood donors. No sociodemographic or clinical characteristics are provided for either the RA patients or the RF positive healthy controls, so we cannot judge the comparability of these two groups. The population of Italian blood donors is self-selected and likely to have a younger mean age.
Borque et al. (1991) conducted a case-control study comparing anti-HCV positivity in 30 RA patients and 40 RF negative carriers of chronic broncho-pneumonia with normal serum immunoglobulin values. The rationale for the selection of chronic broncho-pneumonia patients as a control group is not presented. No sociodemographic characteristics are provided for either the RA patients or controls and as such we cannot judge the comparability of these two groups. However, the principal aim of the study appeared to be to assess whether or not gamma immunoglobulin interferes with anti-HCV immunoassay by mimicking a positive value in some cases.
Congia et al. (1996) conducted a cross-sectional study assessing the prevalence of arthritis amongst 314 HCV positive and 106 HCV negative thalassemia major patients in Italy. Sociodemographic characteristics were not provided for HCV positive versus HCV negative patients, and neither were these factors considered in the analysis of the findings, so we are unable to judge the validity of the results of this study.
D'Amico et al. (1996) conducted a case-control study comparing 49 RA patients with 83 osteoarthritis patients from the same geographic region of Italy. Sociodemographic data other than age and gender was not reported in this study therefore we cannot judge the comparability of these two groups.
De Vita et al. (2002) compared the presence of arthralgia/arthritis in a very small sample of HCV positive (n = 12) compared to HCV negative (n = 50) Sjoegren's Syndrome patients in Italy. Significant differences ($P < 0.05$) were observed in mean age (69 versus 56 years) and presence of liver disease (50% versus 2%) in HCV positive and negative patients, rendering comparison between the two groups unsafe.
Gharagozloo et al. (2001) carried out a case-control study comparing anti-HCV positivity in 30 chronic rheumatoid arthritis patients as compared with three groups comprised of patients with different diseases: essential mixed cryoglobulinaemia patients (n = 42); multiple myeloma patients (n = 45) and chronic lymphocytic leukaemia patients (n = 23). The 30 chronic rheumatoid arthritis patients were intended as controls in this study. Comparing the prevalence of HCV positivity in patients with various diseases, all of which may be caused by HCV, does not provide results which are pertinent to this review (other than comparing the relative risk of HCV infection for each disorder).

Guennoc et al. (2009) conducted a cross-sectional study comparing the prevalence of anti-HCV antibodies in 808 of 813 recent-onset arthritis French patients with that in the French general population as described by Dubois et al. (1997). Guennoc et al. (2009) defined arthritis as definite or probable clinical diagnosis of rheumatoid arthritis or a diagnosis of undifferentiated arthritis with a potential for progressing to RA according to 1987 ACR criteria. However the authors state that there was 'no particular definition' of probable or undifferentiated RA. It should also be noted that since this study employs data relating only to anti-HCV antibody positivity, the assumption must be made that HCV positive patients have past and/or active infection. The sample of recent-onset patients had a mean age of 48 and were predominantly female (approximately 77%) and therefore a valid comparison with the general population cannot be made. However, the principal aim of this study was to evaluate the utility of routine HCV serological testing for the diagnosis of recent-onset polyarthritis.
Maillefert et al. (2002) conducted a case-control study comparing anti-HCV and HCV RNA positivity in 309 rheumatoid arthritis patients with that of the French general population as described by Dubois et al. (1997). The sample of rheumatoid arthritis patients had a mean age of 54 and was predominantly female (75%), so a valid comparison with the general population cannot be made.
Rivera et al. (1999) conducted a case-control study comparing anti-HCV and HCV RNA positivity in 303 patients with RA and 315 first-time blood donors in Spain. There was a significant disparity between the rheumatoid arthritis patients and blood donors with respect to age (58.3 ± 13.0 versus 33.4 ± 11.7 years) and gender balance (78% versus 33% female).
Yucel et al. (2005) performed a backward logistic regression analysis incorporating gender, age, duration of dialysis, cause of renal failure, hepatitis B infection, HCV infection and various laboratory parameters to determine the association between these factors and the prevalence of arthralgia in 284 of 344 chronic haemodialysis patients (32% anti-HCV-positive). They found 'a correlation' between arthralgia and anti-HCV positivity ($p < 0.001$). It should be noted however, that smoking, socio-economic status and liver disease severity were *not* considered in their analysis and as a result we cannot place a great deal of confidence in these findings. Furthermore, since the results are presented with respect to anti-HCV positivity, the study should be thought of as examining the relationship between past and/or active infection rather than chronic infection. In addition, the sample in this study was composed entirely of patients with end stage renal disease, thus limiting generalisability to other populations. Furthermore, of 30 patients who experienced painful, swollen joints after starting haemodialysis, only 12 underwent synovial fluid analysis, revealing that 3 had septic arthritis and 5 tested positive for monosodium urate crystals, suggestive of gouty arthritis. Given that a significant correlation was found between uric acid > 7mg/dl and the presence of arthritis, and that patients on long-term haemodialysis tend to have hyperuricaemia, HCV infection may not be implicated in a number of cases of arthritis within this patient population. Therefore, we have relied upon

the findings of Hsu et al. (2003) in order to determine the association between arthritis and HCV infection.

Table A4.12: Fibromyalgia: studies at high risk of bias (n = 6)

De Vita et al. (2002) compared the presence of FS in a very small sample of HCV positive (n = 12) compared to HCV negative (n = 50) Sjoegren's Syndrome patients in Italy. Significant differences (P < 0.05) were observed in mean age (69 versus 56 years) and presence of liver disease (50% versus 2%), rendering comparison between the two groups unsafe.
Goulding et al. (2001) assessed the prevalence of FS in a cross-sectional study of 77 Irish patients with HCV infection compared with that of the general population as reported by Wolfe et al. (1995). A comparison was made between mean number of tender points in HCV positive individuals infected via contaminated anti-D immunoglobulin, HCV positive individuals infected via injection drug use, and 25 age and sex matched controls. Sociodemographic characteristics other than age and sex were not reported for comparison groups, so we were unable to judge comparability with respect to important confounders.
Kandemir et al. (2006) compared mean number of tender points and pain scores of 40 Turkish HCV infected women with that of age and sex matched fibromyalgia patients and healthy controls. The lack of reporting with regard to the selection of patients and sociodemographic characteristics (other than age and body mass index) provided insufficient information on which to judge the generalisability of the results, or the comparability of comparison groups.
Kozanoglu et al. (2003) evaluated the presence of FS in 95 patients with chronic HCV infection and 95 healthy controls in Turkey. The lack of reporting with regard to the selection of patients and sociodemographic characteristics (beyond age, sex and education) provided insufficient information on which to judge the generalisability of the results, or the comparability of comparison groups.
Narvaez et al. (2005) investigated the prevalence of HCV infection in a case-control study of 115 patients (mean age 45 ± 10, 91% female) with FS and compared it with the prevalence of HCV infection in the general population of Catalonia, Spain. In recognition of the fact that the prevalence of anti-HCV in the general population increased with age, comparisons were made with different age groups (25-44 years) and (45-65 years). However, it was unclear whether or not the gender balance had been addressed, as the community-based seroepidemiological studies from which the general population data was derived could not be retrieved in the time available.
Rivera et al. (1997) conducted both a case-control study of the prevalence of HCV infection in 122 FS patients in comparison with matched rheumatoid arthritis (RA) patients, and a cross-sectional study of the prevalence of FS in 58 chronic hepatitis hospital hepatology unit patients compared with 58 age and sex-matched patients

attending hospital general surgery unit. Since there is a possible association between RA and HCV infection, the findings of the case-control study do not provide information pertinent to this review beyond comparing the relative prevalence of HCV infection in these two populations. The cross-sectional study matched patients and controls for age and sex but did not report on other confounders with the potential to bias the findings.

Table A4.13: Miscellaneous pain outcomes: studies at high risk of bias (n = 2)

Barkhuizen et al. (1999) compared musculoskeletal pain in liver disease patients with and without HCV infection. However, clinical and sociodemographic factors were not presented for comparison groups, nor addressed in the analysis. Although questionnaires and pain diagrams were scored by a rheumatologist blinded to hepatic diagnoses and HCV status, a validated tool does not appear to have been used to assess self-reported pain.
Isaacs et al. (2013) note that only a small number (approximately one quarter) of the 118 HCV patients in their study had extrahepatic symptoms. Changes in chronic widespread pain were compared between those achieving and not achieving sustained viral clearance. Insufficient information is provided to determine the comparability of these two groups. The authors suggest that a larger study with a control group and longer follow-up is needed in order to validate their results. In addition, 77.8% of the 63 patients for whom the route of infection was known were PWID, thus limiting generalisability to other populations.

Appendix 5: Interpretation of depression/anxiety scores

Beck Anxiety Inventory (BAI)

This tool is useful for measuring prolonged state anxiety rather than trait anxiety. Its maximum score is 63 points, with grading of anxiety as follows:

0-7: minimal or no anxiety

8-15: mild anxiety

16-25: moderate anxiety

25-63: severe anxiety

http://learners.ncu.edu/syllabus/download_file.asp?syllabus_rr_id=144846 (accessed 30 June 2014)

Beck Depression Inventory (BDI)

The BDI is recommended for use in assessing depressive symptomatology. It yields a total score of 63, with higher scores indicating more severe depression. Danoff et al. (2006) used a BDI scale with values 0-9 indicating no depression, 10–18, mild to moderate, 19-29, moderate to severe and 30 or more severe depression.

http://learners.ncu.edu/syllabus/download_file.asp?syllabus_rr_id=144846 (accessed 30 June 2014)

Center for Epidemiologic Studies Depression Scale (CES-D)

CES-D is used to detect depressive symptomatology. Its use in HCV populations has been demonstrated (Clark et al. 2002). Scores of over 16 points on the CES-D indicate the presence of depressive symptomatology.

http://cesd-r.com/cesdr/ (accessed 30 June 2014)

Depression, Anxiety and Stress Scales (DASS)

The DASS scale is used to detect negative emotions of depression, anxiety and stress. Scores of 0 to 9 points indicate no depression; 10 to 13 mild depression; 14 to 20 moderate depression; and 21 points or greater clinically significant depression.

http://www.acpmh.unimelb.edu.au/site_resources/TrainingInitiativeDocuments/follow-up/DASS.pdf (accessed 30 June 2014)

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)

The DSM-IV criteria establish a ‘yes’ or ‘no’ diagnosis of depression or anxiety. It diagnoses a wide range of depression, from major depressive disorders to mild dysthymic episodes.

http://www.dnalc.org/view/2222-DSM-IV-criteria-for (accessed 30 June 2014)

Hospital Anxiety and Depression Scale (HADS)

HADS was developed to be used to diagnose depression and anxiety in both hospital and community settings. Scores range from 0 to 21; values of more than 11 points indicate depression or anxiety.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC183845/ (accessed 30 June 2014).

The interpretation of HADS differed across studies. For example, employing the HADS, Ashrafi et al. (2012) used the 75th centile values as a cut-off point for determining depression or anxiety, with values above the 75th centile indicating 'more' depression or anxiety, and those below the 75th value indicating 'less'. Alavian et al. (2007) considered scores of 11 or more indicative of depression or anxiety. Lowry et al. (2010) did not report their clinical interpretation of HADS scores.

Hamilton Depression Rating Scale (HDRS)

Only one study utilised the HDRS (Von Giesen et al. 2004). This screening tool is used to detect depression in hospital patients, where a value of 0 to 7 indicated no depression, 8 to 19 mild and 20 or more moderate to severe depression.

https://pdbp.ninds.nih.gov/assets/crfs/Hamilton%20Depression%20Rating%20Scale%20(HDRS).pdf (accessed 30 June 2014)

Patient Health Questionnaire (PHQ-9)

The PHQ-9 indicates a range of depression:

0-4: none

5-9: mild

10-14: moderate

15-19: moderately severe

20-27: severe.

Lee et al. (2013) interpreted scores to determine whether patients had mild, moderate or suicidal depressive symptoms, but the interpretation of test scores was not reported. It should be noted that the PHQ-9 was developed to monitor depressive symptoms during treatment, not to diagnose depression.

http://www.patient.co.uk/doctor/patient-health-questionnaire-phq-9 (accessed 30 June 2014)

Zung Self-rating Depression Scale (SDS)

This test is used to assess affective, psychological and somatic symptoms of depression. Scores range from 20 to 80 points. Those greater than 50 points indicate clinically significant depression, with scores of 70 and over indicating severe depression.

http://www.who.int/substance_abuse/research_tools/zungdepressionscale/en/ (accessed 30 June 2014)

State-Trait Anxiety Inventory (STAI)

The STAI is normally used to diagnose state and trait anxiety and to distinguish it from depression. Scores range from 20 to 80 points, with scores greater than 40 points indicating clinically significant anxiety.

http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/trait-state.aspx (accessed 30 June 2014)

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