Review

Prevalence of hepatitis C virus infection among key populations in China: A systematic review

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A B S T R A C T

Background and aim: Chronic hepatitis C is a major global health challenge. China has the world's largest burden of hepatitis C and related liver disease, with several groups having an increased risk of acquiring hepatitis C virus (HCV) infection. We undertook a systematic review in Chinese and English literature to determine the seroprevalence of anti-HCV among men who have sex with men (MSM), sex workers, people who use drugs (PWUD) and migrant workers in China.
Methods: We searched three Chinese databases (CNKI, Wanfang and Chongqing VIP Information) and four English databases (Pubmed, EMBASE, Global Health and CINAHL) for studies published between 2010 and 2015. Included were 89 studies for MSM, 112 for sex workers, 11 for migrant workers, 94 for people who inject drugs (PWID) and 67 for non-injectors. Random-effect models pooled estimates of anti-HCV seroprevalence in each population and a meta-regression model examined the relationship between anti-HCV seroprevalence and injecting drug use.
Results: The overall pooled seroprevalence of anti-HCV among MSM was 0.67% (CI 95 0.51–0.86); for sex workers 0.65% (CI 95 0.53–0.77); for migrant workers 0.48 (CI 95 0.20–0.85); for IDUs 72.41% (CI 95 68.71–75.97); among non-injectors 25.07% (CI 95 21.51%–28.80%). Our meta-regression model predicted that the seroprevalence of anti-HCV among PWID increased by 8.6% for each 10% increase seroprevalence of reporting ever having injected drugs.
Conclusions: Overall, seroprevalence of HCV infection is high among PWUD, especially those who inject. Lower HCV seroprevalence (<1%) was found among MSM, sex workers and migrant workers. Our estimates for IDU seroprevalence are higher than that from the national surveillance system, though estimates for other at-risk populations are similar.
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Introduction

Chronic hepatitis C (HCV) is a major global health challenge. It is estimated that 71 million people are living with chronic HCV infection (Polaris Observatory HCVC, 2017). Long term HCV infection can lead to cirrhosis, hepatocellular carcinoma and early death. Hepatitis C related mortality is estimated at 700 000 annually (Vos et al., 2015), virtually all from chronic infection. China has the highest burden of HCV in the world (Polaris Observatory HCVC, 2017), with an estimated 8.9 million people living with chronic HCV infection, and the largest burden of liver – 51% of all global liver cancer deaths (GBD, 2015).

In China, there have been a number of national serosurveys and estimates of HCV seroprevalence over the last 25 years. In 1996, the overall seroprevalence of anti-HCV antibody nationally was estimated at 3.2% (Xia et al., 1996), falling to 0.43% in 2006 (Chen et al., 2011). This latter survey excluded institutionalized persons, and migrant populations who had lived in the sampled areas for less than six months. While it is likely that reduced transmission contributed to reduction in estimated national seroprevalence, it is also hypothesized that improved HCV test specificity contributed to this lower estimate.

The epidemiology of HCV can be explained by unsterile medical injections (Frank et al., 2000; Drucker et al., 2001; Kermode, 2004; Miller and Abu-Raddad, 2010) which are often administered for unnecessary reasons, unsafe blood and blood products injections and injecting drug use (Nelson et al., 2011a). The risk of HCV transmission from unsafe blood injections has reduced substantially over the last 20 years, particularly since the introduction of nucleic acid testing in blood banks by the Chinese government (Shi et al., 2014).

Hepatitis C surveillance in China includes annual cross sectional surveys and reporting of routine health examination data from the general population. In addition, there are now 1888 sentinel sites for HIV targeting at-risk populations which also report HCV data (Qin et al., 2015). Both acute and chronic hepatitis C are notifiable infections across China, as detailed in the Law of the People's Republic of China and the Prevention and Treatment of Infectious Disease (2004).

To investigate the seroprevalence of chronic hepatitis C infection among at-risk populations in China, we undertook a systematic review of Chinese and English language published literature including surveillance and investigator driven studies. We included migrant workers, sex workers, men who have sex with men (MSM), and people who use drugs (PWUD), which includes non- and injecting drug use, in our analysis.

Methods

We conducted the review in Chinese and English. We searched the three major Chinese scientific databases (Chinese National Knowledge Infrastructure (CNKI), Wanfang and Chongqing VIP Information (CQVIP)) and four English databases (Pubmed, EMBASE, Global Health (GH) and Cumulative Index to Nursing and Allied Health Literature (CINAHL)) for articles published between January 1st 2010 and July 1st 2015. These databases were chosen for their quality and prominence in Chinese scientific publications.

The search syntax was identical in Chinese and English. The full search syntax is included in supplementary materials and included terms relating to "hepatitis", "prevalence" "incidence" or terms relating to serosurvey and terms relating to hepatitis seromarkers as well as the key population of interest. Included key populations were sex workers, MSM, migrant workers and PWUD (including those who inject). Migrant workers are defined as those whose hukou, the household registration system in China, is different from the province they are working or looking for work. To increase the specificity of the search in Chinese, we first tested the strategy among the Chinese databases and popular Chinese search engines, identifying possible variations of Chinese terms relating to viral hepatitis and key populations. We then included all synonyms, acronyms and closely related terms identified from this pilot search in the final search syntax.

We merged all search hits by population of interest. Duplicate entries were removed. Given the large number of hits, titles and abstracts were initially screened separately by two reviewers, with a third reviewer who was consulted to resolve uncertainties. Full text articles were obtained and screened in either Chinese or English by the three reviewers. Given the large numbers of studies from Chinese literature, we excluded studies with total sample sizes of less than 100. Included studies needed to report at least one cross-sectional assessment of anti-HCV seroprevalence.
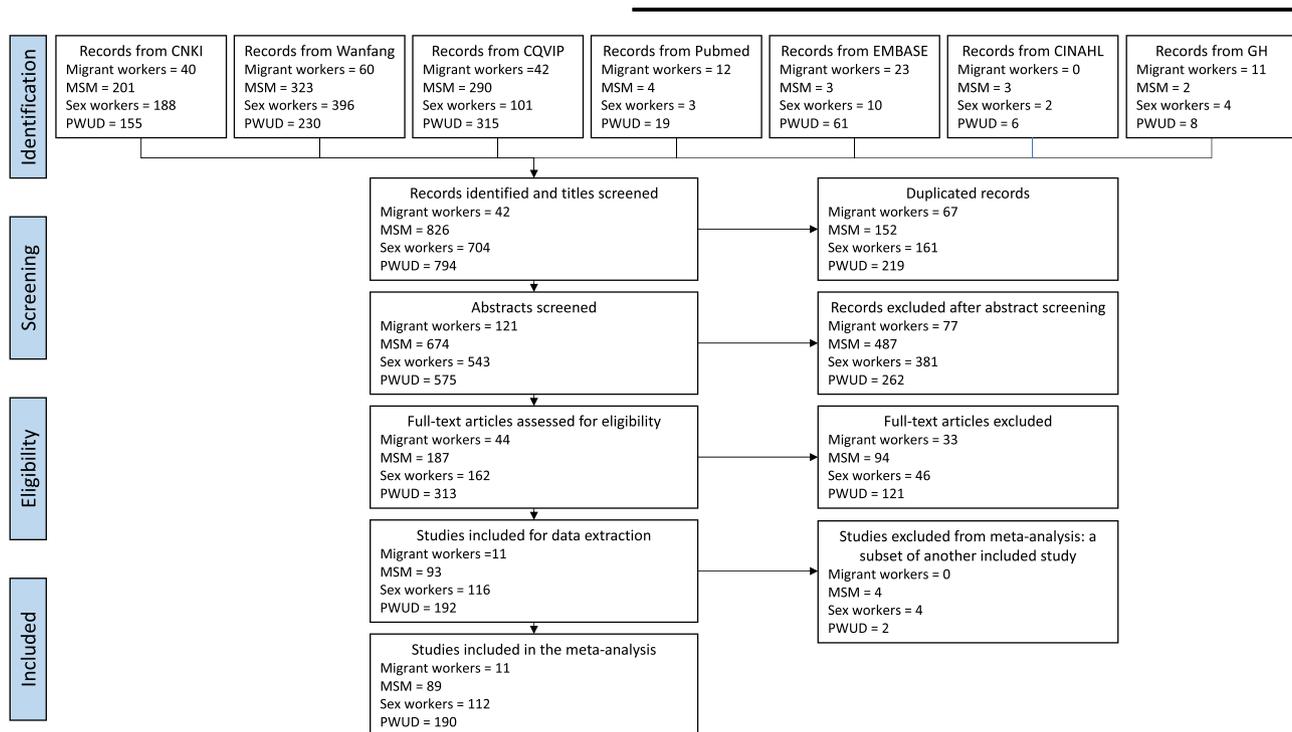
To reduce potential risks of selection bias, we excluded studies among specific groups such as those seeking HCV treatment or samples exclusively among people living with HIV. The following variables were extracted: location, year surveyed, age, sampling method, sample size, number of HCV positive cases, anti-HCV seroprevalence, seroprevalence of HCV RNA viraemia, co-infection with HIV or HBV, risk acquisition factors, and confidence interval if reported. In addition, for PWUD, we extracted the seroprevalence of injecting drug use and anti-HCV seroprevalence among the sample of people who inject drugs (PWID) and non-injectors if reported.

Meta-analysis of anti-HCV seroprevalence was performed for each specific key population and subgroups using Stata 13 (StataCorp LP, Texas). Studies reporting seroprevalence in multiple years were included in the meta-analysis as pooled single point estimates. Reports from the national surveillance system were excluded from the meta-analyses since there were many publications of data samples taken from the national surveillance system in the Chinese literature, leading to overlapping reporting of results. We could not assess the extent of overlap for each study based on published information. A random-effects model was selected to pool the proportion of persons testing positive for anti-HCV from all the study sites and compare to reports from the national surveillance system. Freeman-Tukey double arcsine transformation was used in all models to stabilize variance as many studies reported seroprevalence of close to 0 or 1 (Nyaga et al., 2014).

In the analysis, we stratified sex workers by location of sampling, i.e., high-end, mid and low-end establishments, as the location of service could influence HCV risk. For PWUD, random-effect models were constructed separately for PWID and non-injectors. A meta-regression model was developed to examine the association between anti-HCV seroprevalence and proportion of PWUD that had ever injected drugs in the samples. Studies exclusively conducted among amphetamine and other people who use "non-traditional drug" were excluded from meta-regression, because the drug administration route and average length of drug use differed substantially from the profile of other PWUD, most of

whom reported heroin use. Studies exclusively sampling PWID were also excluded from the regression model as within these studies injecting history was often not reported and we could not clearly determine whether the whole sample consisted of PWUD.

socioeconomic tier defined by the studies themselves: high, middle and low. Of the studies included for analysis, five articles reported disaggregated data among high, middle, and low socioeconomic status sex workers. Two articles specifically

Identification

Records from CNKI	Records from Wanfang	Records from CQVIP	Records from Pubmed	Records from EMBASE	Records from CINAHL	Records from GH
Migrant workers = 40	Migrant workers = 60	Migrant workers = 42	Migrant workers = 12	Migrant workers = 23	Migrant workers = 0	Migrant workers = 11
MSM = 201	MSM = 323	MSM = 290	MSM = 4	MSM = 3	MSM = 3	MSM = 2
Sex workers = 188	Sex workers = 396	Sex workers = 101	Sex workers = 3	Sex workers = 10	Sex workers = 2	Sex workers = 4
PWUD = 155	PWUD = 230	PWUD = 315	PWUD = 19	PWUD = 61	PWUD = 6	PWUD = 8

Screening

Records identified and titles screened
Migrant workers = 42
MSM = 826
Sex workers = 704
PWUD = 794

Duplicated records
Migrant workers = 67
MSM = 152
Sex workers = 161
PWUD = 219

Abstracts screened
Migrant workers = 121
MSM = 674
Sex workers = 543
PWUD = 575

Records excluded after abstract screening
Migrant workers = 77
MSM = 487
Sex workers = 381
PWUD = 262

Eligibility

Full-text articles assessed for eligibility
Migrant workers = 44
MSM = 187
Sex workers = 162
PWUD = 313

Full-text articles excluded
Migrant workers = 33
MSM = 94
Sex workers = 46
PWUD = 121

Included

Studies included for data extraction
Migrant workers = 11
MSM = 93
Sex workers = 116
PWUD = 192

Studies excluded from meta-analysis: a subset of another included study
Migrant workers = 0
MSM = 4
Sex workers = 4
PWUD = 2

Studies included in the meta-analysis
Migrant workers = 11
MSM = 89
Sex workers = 112
PWUD = 190

Results

Here we report at-risk groups separately according to the methods above.

Men who have sex with men

The initial search identified 814 records illustrated in Figure 1. After deduplication, 674 abstracts were screened and 187 full-text articles were assessed for eligibility of data extraction. We extracted data from 93 studies that met inclusion criteria. Four studies were further excluded because they are subsets of included studies, leaving 89 studies included in the final analysis. The anti-HCV pooled seroprevalence in MSM was 0.67% (95% CI: 0.51%–0.86%), comparable to that estimated through the national surveillance system (0.7%) between 2009 and 2012 (Wang et al., 2013).

Sex workers

The initial search identified 704 records illustrated in Figure 2. After deduplication, 543 titles and abstracts were reviewed, and full-text articles were obtained for 162 studies. We extracted data from 116 studies meeting the inclusion criteria. After removing studies which re-published already published data, 112 studies were included in the meta-analysis. The pooled seroprevalence of anti-HCV seroprevalence in sex workers was 0.65% (95% CI: 0.53%–0.77%). This is slightly lower than the reported seroprevalence of the national surveillance system at 0.8% between 2009 and 2012 (Wang et al., 2013). Following this, we undertook an additional analysis of the seroprevalence of anti-HCV among sex workers by

sampled mid-tier sex workers, while 13 studies sampled lower-tier sex workers (Liu et al., 2014). The pooled seroprevalence of anti-HCV among sex workers was 1.37% (95% CI: 0.80%–2.07%) for low-tier (18 studies) shown in Figure 4, 0.40% (95% CI: 0.08%–0.90%) for mid-tier (7 studies) and 0.41% (95% CI: 0.00%–1.30%) for high-tier (5 studies) shown in Figure 5.

Migrant workers

The initial search identified 142 records (Figure 3). After removing the duplicates, 121 abstracts were screened and 44 full-text articles were assessed for eligibility of data extraction. Data was extracted from 11 studies and all were included in the meta-analysis. The anti-HCV pooled seroprevalence among migrant workers was 0.48% (95% CI: 0.20%–0.85%). This was similar to the national surveillance system estimated seroprevalence of 0.5% among male migrant workers between 2009 and 2012 (Wang et al., 2013).

People who use drugs

The initial search identified 794 records (Figure 4). Data was extracted from 192 studies. We further excluded two studies reporting national surveillance data, 84 studies reporting anti-HCV seroprevalence among PWID and 67 studies reporting anti-HCV seroprevalence among non-injectors. Among PWID, the pooled seroprevalence was 72.41% (95% CI: 68.71%–75.97%), higher than the reported 63.2% seroprevalence reported by the national surveillance system 2009 to 2012 (Wang et al., 2013). The pooled seroprevalence of anti-HCV among non-injectors in this review was 25.07% (95% CI: 21.51%–28.80%). Anti-HCV seroprevalence among non-injectors was not reported in the national surveillance system.
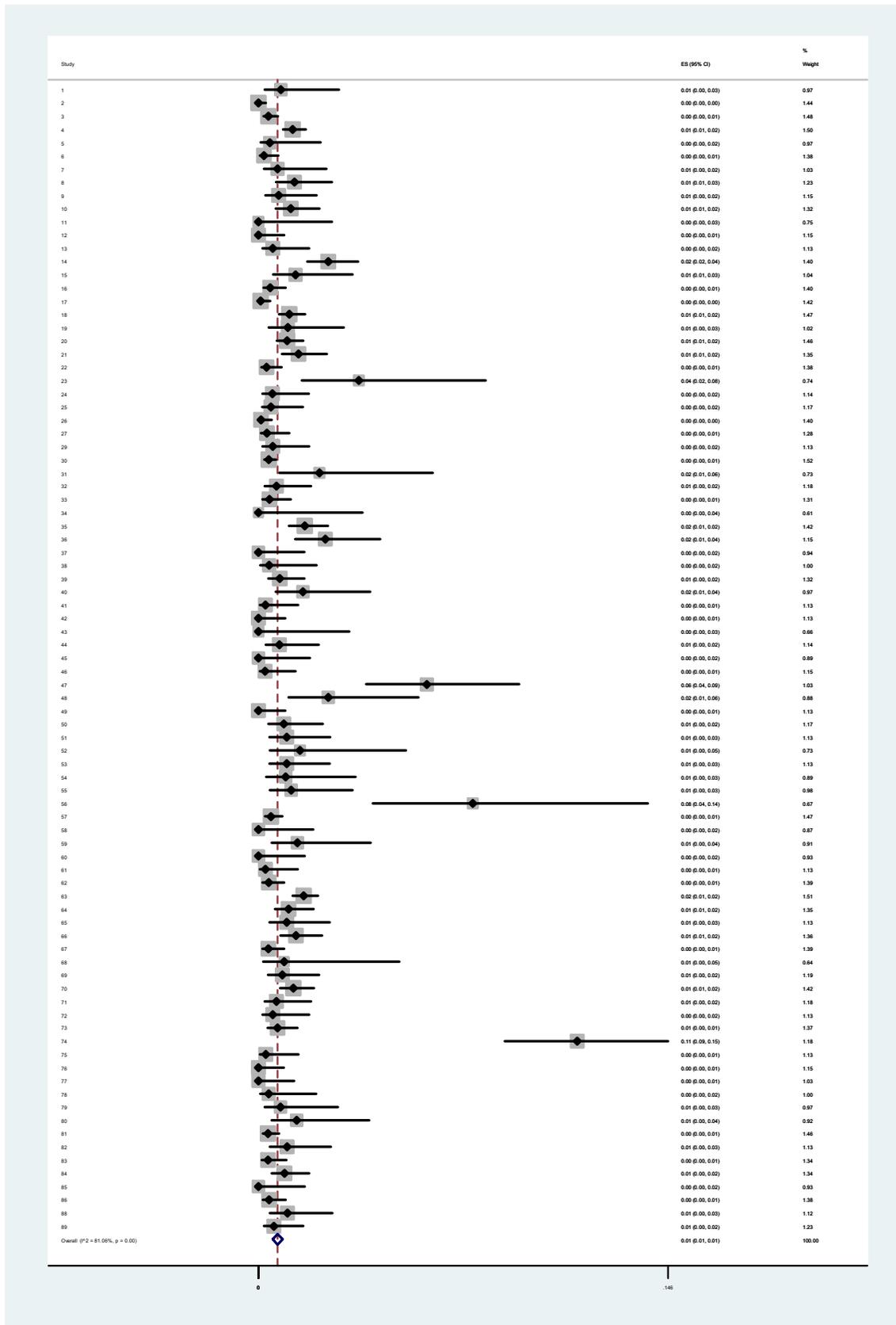
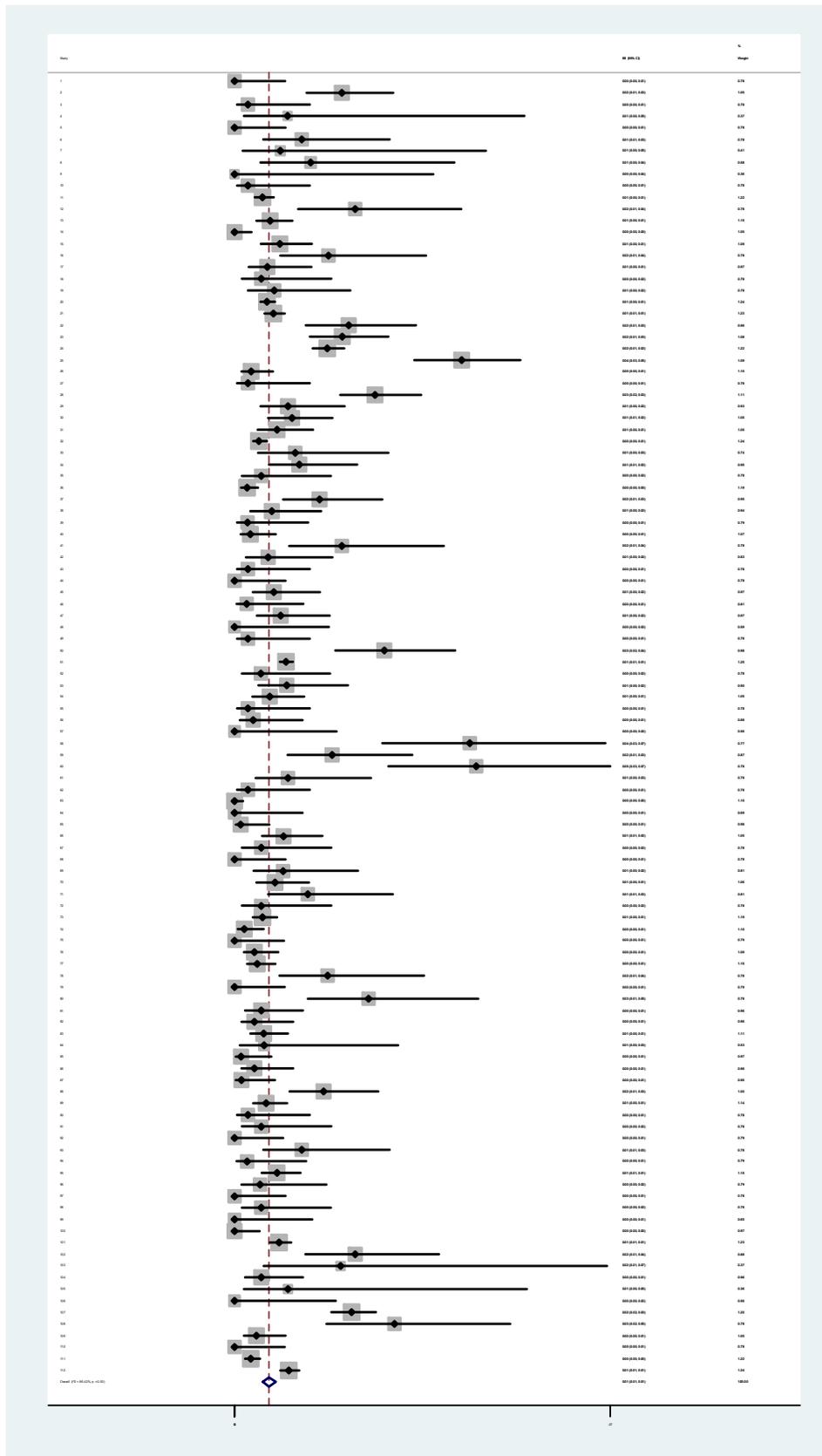**Figure 1.** Forest charts. Men who have sex with men.
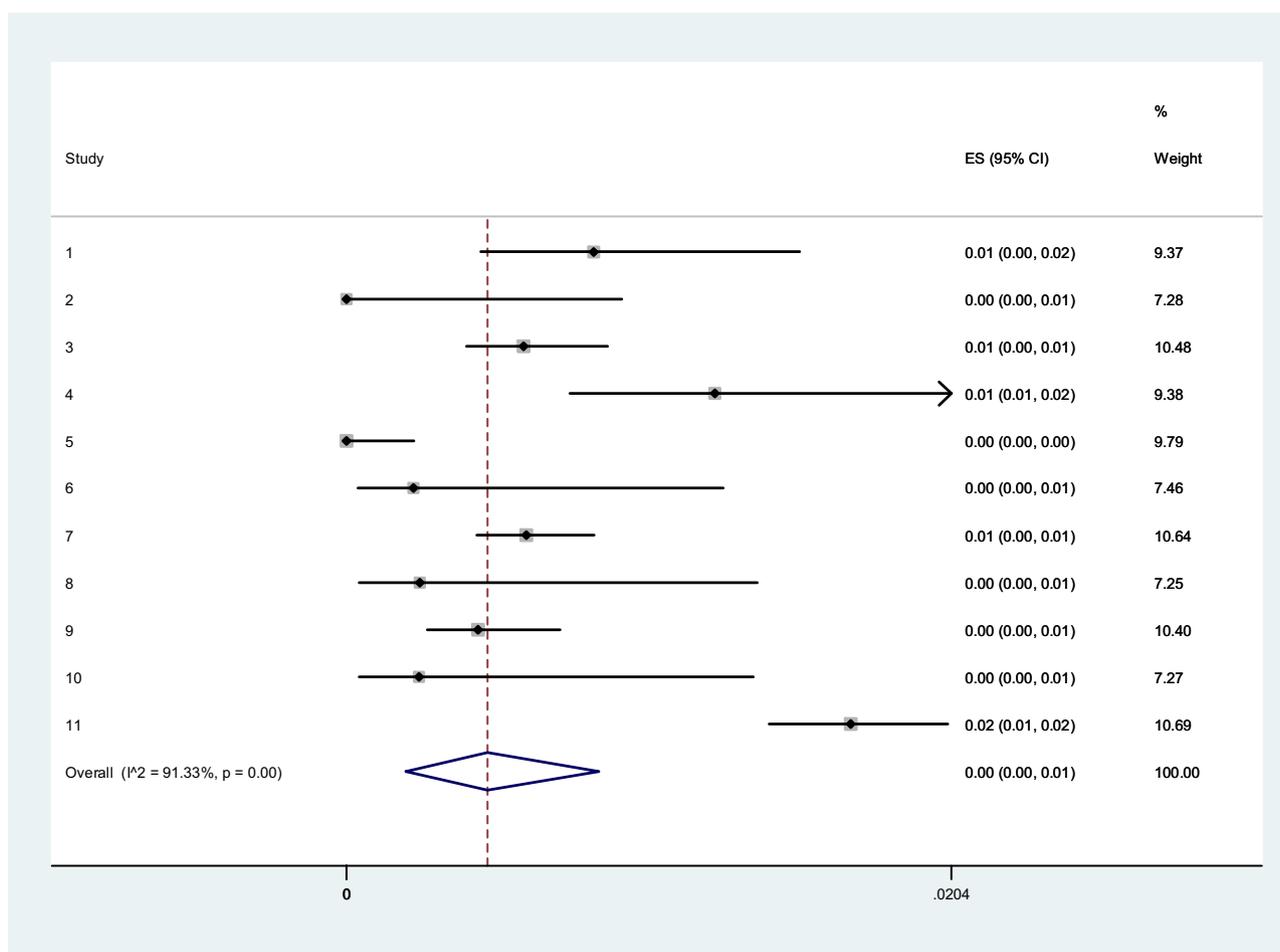
Figure 2. Sex workers.

Figure 3. Migrant workers.

To examine the relationship between the seroprevalence of injecting drug use and anti-HCV among study populations, we excluded the national surveillance study and studies exclusively sampling new drug users and PWUD. In all, 117 studies reported both seroprevalence of injecting drug use and anti-HCV and these were included in the meta-regression model. The fitted model, shown in Figure 5 (b = 0.86 intercept 0.68 and R^2 = 0.77), showed that for every 10% increase in seroprevalence of ever-injected among all PWUD, the seroprevalence of anti-HCV increases by 8.6%. Using the seroprevalence of injecting drug use among drug using populations as a proxy (in China 54.2% of PWUD were injectors in the 2009–2012 national surveillance system reports), this model predicts that anti-HCV seroprevalence among PWUD to be 47%, slightly higher than the reported anti-HCV seroprevalence of 41.5% reported by the national surveillance system for 2009–2012 (Wang et al., 2013).

Discussion

We examined the seroprevalence of HCV in several at-risk populations in China. To our knowledge this is the first systematic review and meta-analysis to examine HCV seroprevalence among specific at-risk populations in China that complied with western and Chinese literature. The pooled anti-HCV seroprevalence was highest among PWID, which was 72.41% (95% CI: 68,71%–75.97%), while for non-injectors it was 25.07% (95% CI: 21.51%–28.8%). The

pooled seroprevalence of anti-HCV among other at-risk populations was 0.65% (95% CI: 0.53%–0.77%) for sex workers, 0.67% (95% CI: 0.51%–0.86%) for MSM and 0.48% (95% CI: 0.2%–0.85%) for migrant workers. The latter was comparable to the estimated 0.48% general population seroprevalence of anti-HCV based on national surveillance data (Chen et al., 2011). The seroprevalence for each at-risk population is summarized in Table 1. The high seroprevalence of anti-HCV in PWID suggests ubiquitous transmission among this population and an urgent need for concerted prevention and treatment initiatives (Figures 6–9).

As individual level data on injecting and HCV status was not reported in most studies, we used meta-regression techniques to understand the relationship between the seroprevalence of HCV and injecting drug use in study populations. Excluding studies with very low numbers of PWID (i.e. <10% of study population – these studies commonly included large numbers of amphetamine-type stimulant users), for every 10% increase in the seroprevalence of those reporting injecting, there was a corresponding increase in anti-HCV seroprevalence of 8.6%. High HCV seroprevalence among PWID has been demonstrated in many countries across the world (Nelson et al., 2011b). The seroprevalence of anti-HCV in non-injectors across China was estimated at 25%, which was high compared with that found in the global literature (Scheinmann et al., 2007). However, drug use history in the studies was self-reported and could have resulted in underreporting of injection status. In addition, HIV status of these individuals was unknown.
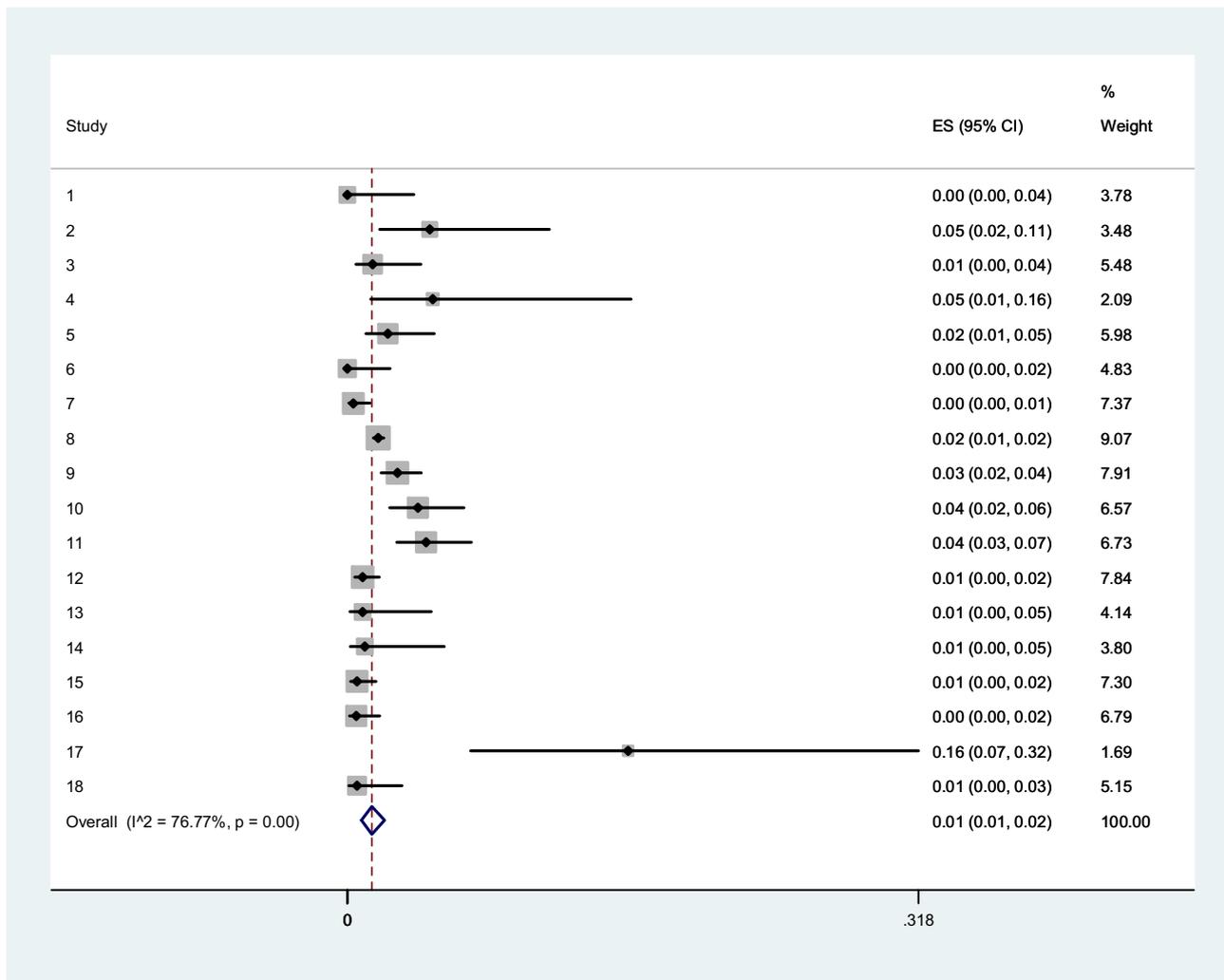
Study	ES (95% CI)	% Weight
1	0.00 (0.00, 0.04)	3.78
2	0.05 (0.02, 0.11)	3.48
3	0.01 (0.00, 0.04)	5.48
4	0.05 (0.01, 0.16)	2.09
5	0.02 (0.01, 0.05)	5.98
6	0.00 (0.00, 0.02)	4.83
7	0.00 (0.00, 0.01)	7.37
8	0.02 (0.01, 0.02)	9.07
9	0.03 (0.02, 0.04)	7.91
10	0.04 (0.02, 0.06)	6.57
11	0.04 (0.03, 0.07)	6.73
12	0.01 (0.00, 0.02)	7.84
13	0.01 (0.00, 0.05)	4.14
14	0.01 (0.00, 0.05)	3.80
15	0.01 (0.00, 0.02)	7.30
16	0.00 (0.00, 0.02)	6.79
17	0.16 (0.07, 0.32)	1.69
18	0.01 (0.00, 0.03)	5.15
Overall ($I^2 = 76.77\%$, p = 0.00)	0.01 (0.01, 0.02)	100.00

Figure 4. Sex workers-low priced venues.

HIV infection is associated with increased risk of sexual transmission of HCV (Terrault, 2002).

Full participation in harm reduction interventions by PWID is associated with reduced odds of HCV transmission among PWID of almost 80% (Turner et al., 2011). Full harm reduction includes high intensity needle and syringe programs (>1 needle per injection per person) and therapeutic dosages of opioid substitution therapy (OST) for opioid-dependent individuals. Methadone maintenance therapy (MMT) is the primary form of OST in China. In some regard, the misconception of MMT as curative treatment lead to increased public support when compared to NSP, the latter being perceived as encouraging drug use. By the end of 2014, there were 184,000 people on MMT across 28 provinces in attending 787 clinics (China NHaFPCotPsRo, 2015) The same reporting mechanism indicated that only 56 000 individuals were accessing NSP across only 14 provinces. Nonetheless, the 814 NSP sites reported distribution to be 196 needles and syringes per injector per year, close to the 2020 Global target of 200 needles and syringes per injector per year, though still less than what is considered the high intensity target. NSP in China has been shown to reduce HIV transmission, drug related harm, as well as being cost-effective (Turner et al., 2011)

Among migrant workers, the seroprevalence of anti-HCV was similar to that estimated nationally for the general population. In 2012, national hepatitis surveillance sentinel sites reported anti-HCV seroprevalence of 0.48% (Wang et al., 2013). While our point estimate was lower, confidence intervals overlap with the national surveillance report estimates. It should be noted that the surveillance was conducted only on male migrant workers. Migration of workers in China is typically from rural to urban areas, smaller to larger cities, and from west to eastern regions. In China, migrant workers are commonly employed in construction, manual labour and the service industry. Although the low HCV seroprevalence among migrant workers seems reassuring, the transient nature of migrant work and mobility is associated with exposure to high risk activities (Zou et al., 2014). In addition, China has a very large migrant worker population, estimated at about 250 million (Zheng, 2015). The eight studies included in the analysis may not have adequately represented the diversity of migrant populations in China.

Overall, FSW had low anti-HCV seroprevalence compared to the general population. However, sex workers from the low socioeconomic tier had higher anti-HCV seroprevalence compared to the higher tiers, which suggests engagement in risk behaviours for
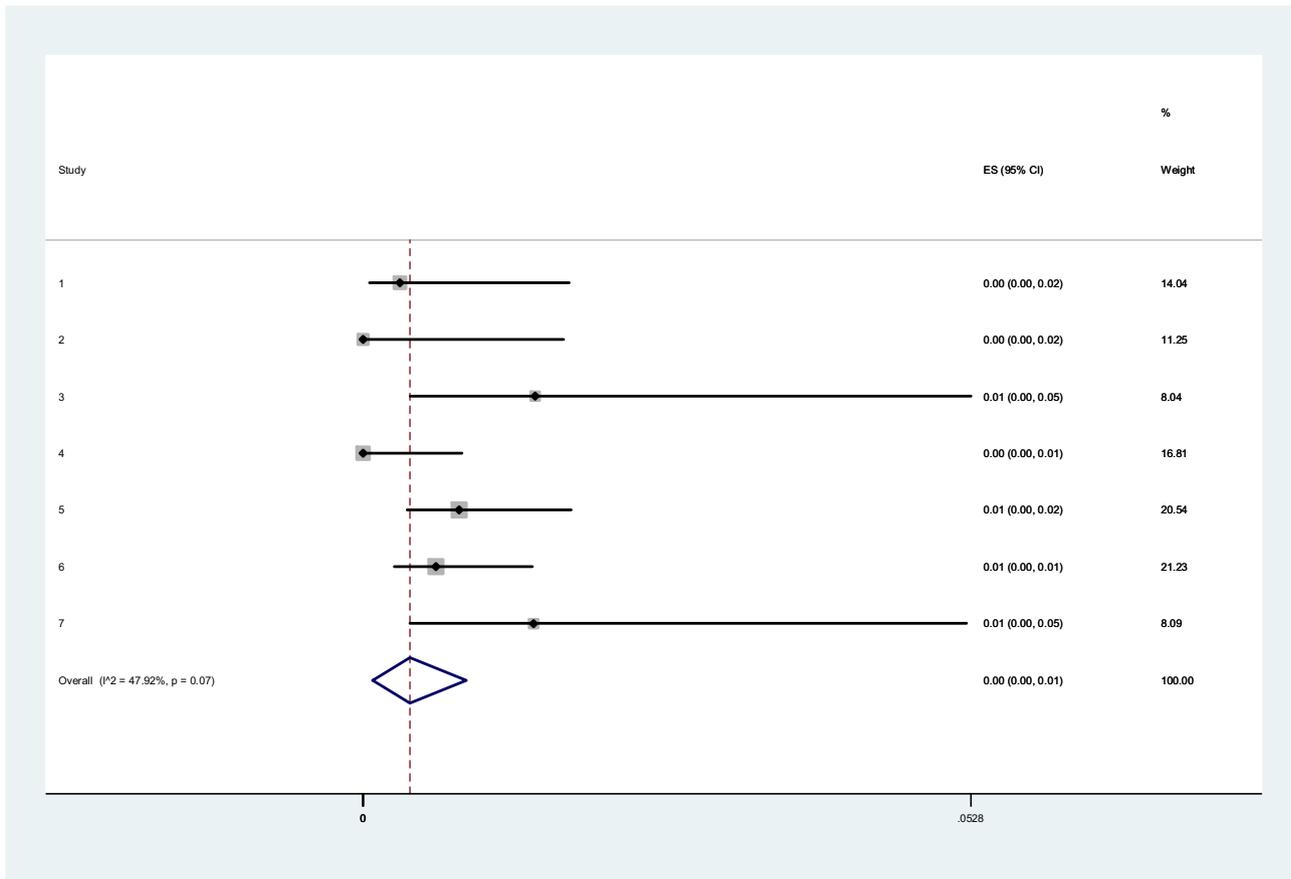
Figure 5. Sex workers-mid-priced venues.

Table 1
Comparison of anti-HCV seroprevalence between the meta-analysis and reported national surveillance system 2009–2012.

Population	2009–2012 surveillance results (%)	Estimate from meta-analysis (%)
MSM	0.7	0.67 (0.51–0.86)
Sex workers	0.8	0.65 (0.53–0.77)
Migrant workers	0.5	0.48 (0.2–0.85)
PWID	63.2	72.41 (68.71–75.97)
Non-injectors	–	25.07 (21.51–28.8)

acquiring HCV. Various factors could contribute to this higher seroprevalence, including injection drug use and sexual transmission of HCV. A large national survey of 827,079 FSW across various socioeconomic tiers across thirty-one provinces in China between 2008 and 2012 found higher inconsistent condoms use among sex workers of the lower socioeconomic tier. The low tier FSW are more likely to engage in risky behaviors, which is shown in the higher percentage of IDU, and have less accurate knowledge of HIV/AIDS (Wang et al., 2014). This puts them at higher-risk of getting HIV, which increases their chance of contracting HCV through unprotected sex.

MSM account for an increasingly large percentage of new HIV infections in China (China NHaFPCotPsRo, 2015; Zhang et al., 2013). Our study suggests that the anti-HCV seroprevalence remains relatively low (0.64%) in this group and comparable to the national estimates of 0.7%. There is little data available on HCV incidence

among MSM in China, however a 2009 study indicated that HCV incidence among MSM in Beijing was low (0.2 per 100 person-year) (Ruan et al., 2009). While HCV is difficult to transmit sexually, HIV infection is associated with sexual transmission of HCV (Breskin et al., 2015). Indeed, HIV incidence among MSM is increasing (Beyrer et al., 2013). While injecting drug use among this population is always a concern, increasing HIV seroprevalence among MSM in China could indicate increased HCV sexual transmission risk (Nehl et al., 2015). Consistent condom use, as well as early diagnosis treatment of HIV in these affected individuals will reduce this risk.

This systematic review included studies reported by the national surveillance system as well as studies of anti-HCV seroprevalence in key populations across China. The pooled estimates generated for migrant workers, men who have sex with men, and sex workers were similar to reported seroprevalence
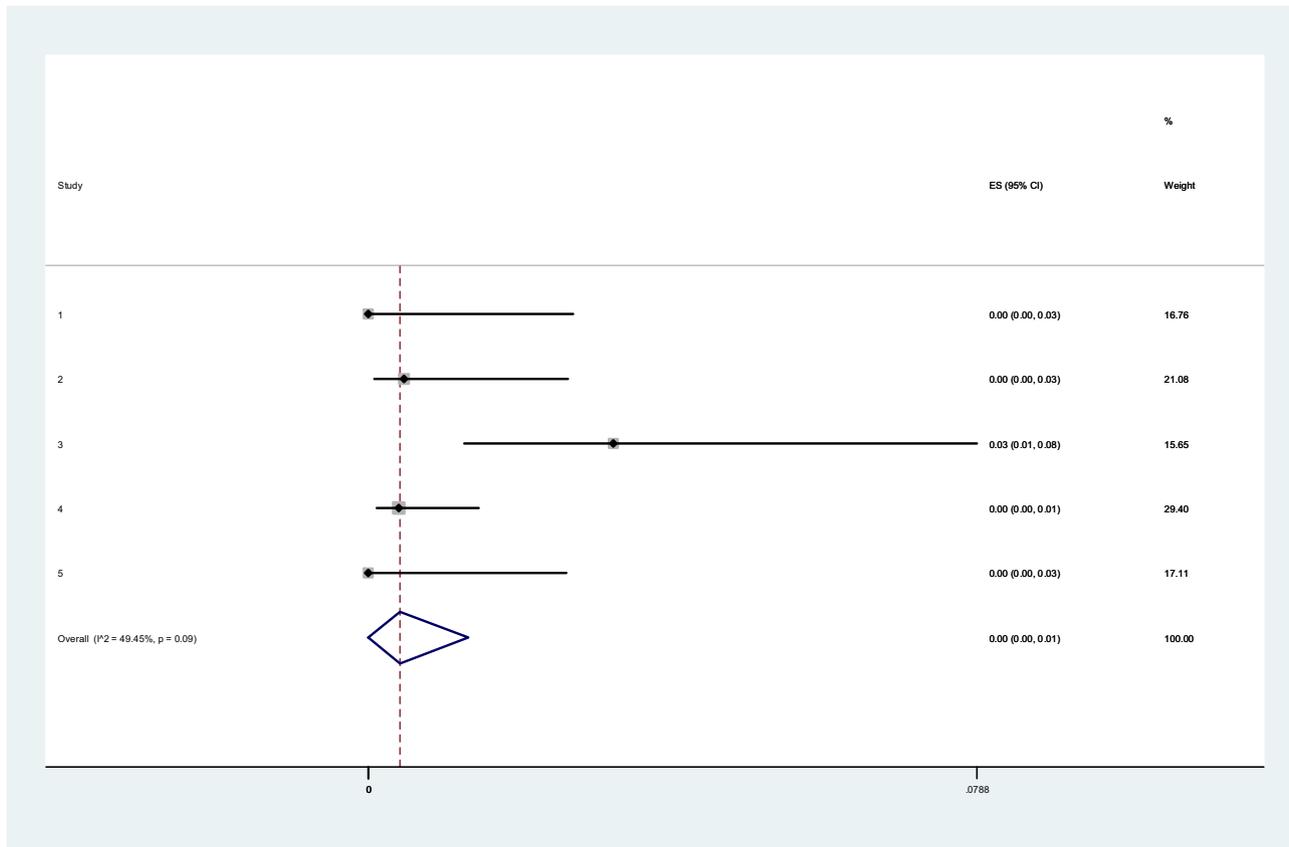
Figure 6. Sex workers high tier.

from the national surveillance system (2009–2012). Among PWUD, the predicted anti-HCV seroprevalence based on meta-regression modeling was slightly higher than that reported by the national system. Since our study included only recently published data on anti-HCV seroprevalence, these findings may reflect a more recent picture of the HCV epidemic in China among selected key populations.

This systematic review of HCV studies in China used both published Chinese and English literature focusing on all key populations. The inclusion of literature from both languages is significant as the vast majority of seroprevalence data from China is published in the Chinese language and therefore not known outside the country. Several global reviews on anti-HCV seroprevalence have been published which include China estimates (Polaris Observatory HCVC, 2017), but these have been drawn from the English language literature. Another strength of the study is that the search strategy was first piloted in the Chinese databases and popular Chinese search engines to identify possible variations of Chinese terms relating to viral hepatitis and key populations. We included all these synonyms, acronyms and closely related words identified in the final search strategy.

This study had a number of limitations. Included studies varied in quality, especially for how results were reported. Most studies failed to describe sampling methods in detail. Age and drug use for studies examining HCV are considered *a priori* variables, however in the Chinese language literature these variables were not always consistently reported. There was geographic limitation as most studies were conducted along the eastern coastal region of China. We identified very few studies from western China. In addition,

even along the east coast, most studies were carried out in the larger urban centers, with few from rural areas. In order to develop recent estimates, this review only examined the period from 2010–2015. Consequently, we were not able examine changes in anti-HCV seroprevalence over time. Finally, here we only report anti-HCV seroprevalence as HCV RNA data was not consistently available. Only 55–85% of individuals with anti-HCV will be viraemic for HCV (i.e. HCV RNA positive indicating current infection) (Organization WH, 2016). The actual number of people living with chronic hepatitis C in these key populations will therefore be lower.

In summary, we found very high HCV seroprevalence among PWID in China, moderately high anti-HCV seroprevalence among reported non-injectors and low anti-HCV seroprevalence among MSM and migrant workers. There was a linear relationship between anti-HCV seroprevalence among PWUD and the sero-prevalence of those ever having reported injecting drugs. The seroprevalence of anti-HCV varied in sex workers and was higher among those employed in the lower socioeconomic tiers of the sector. Our results are consistent with national surveillance data from the preceding years, though our predicted seroprevalence among PWIDs is higher.

Further research is needed to better understand modes of HCV transmission among people with no known history of injecting drug use, and HCV sexual transmission risk among key populations such as sex workers (male and female), MSM and other at-risk groups. Programmatic responses addressing HCV prevention and control in China must include PWUD in order to reduce on-going transmission and the infectious pool of chronic HCV as treatment becomes more widely available. Finally, the higher anti-HCV
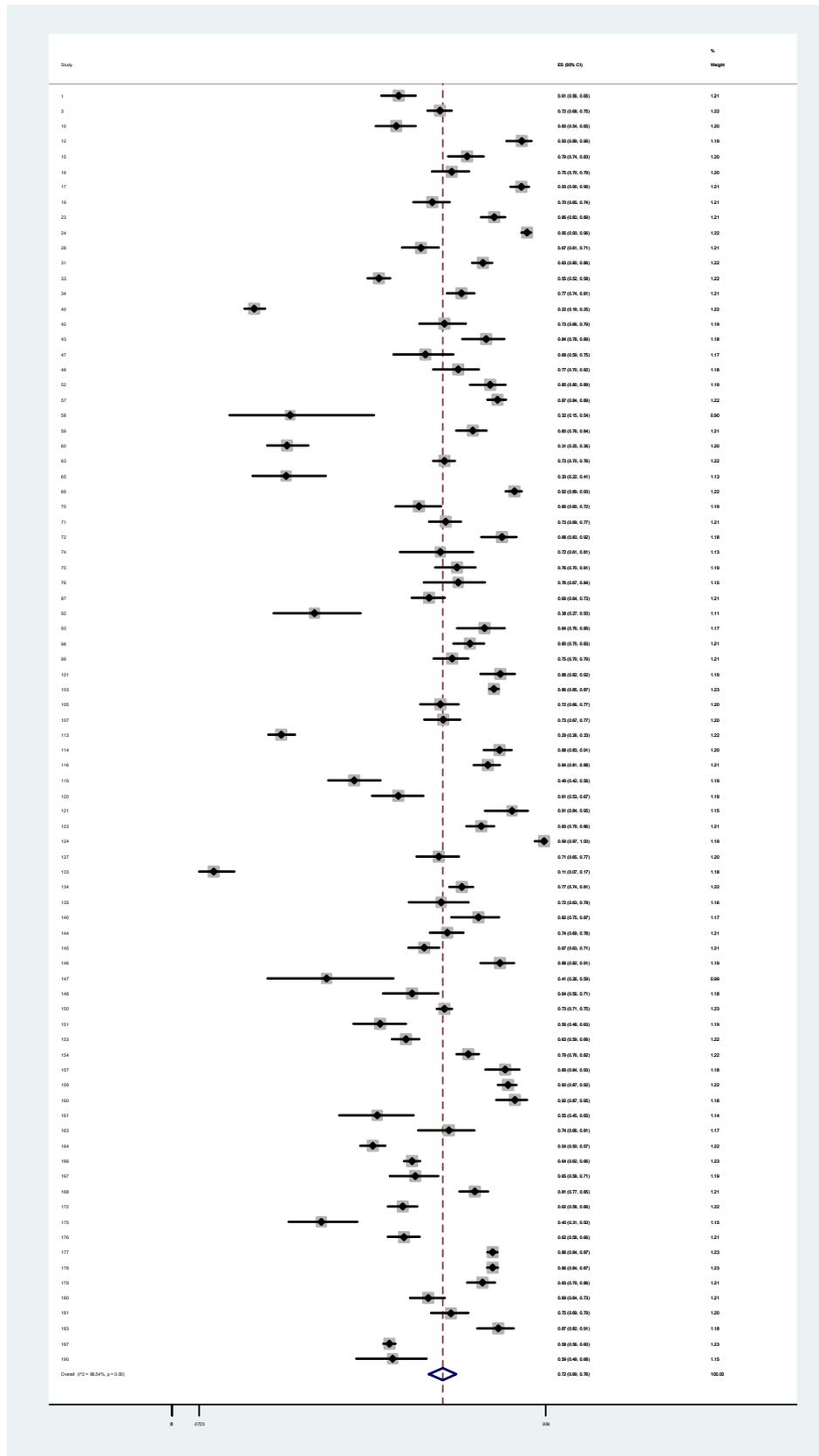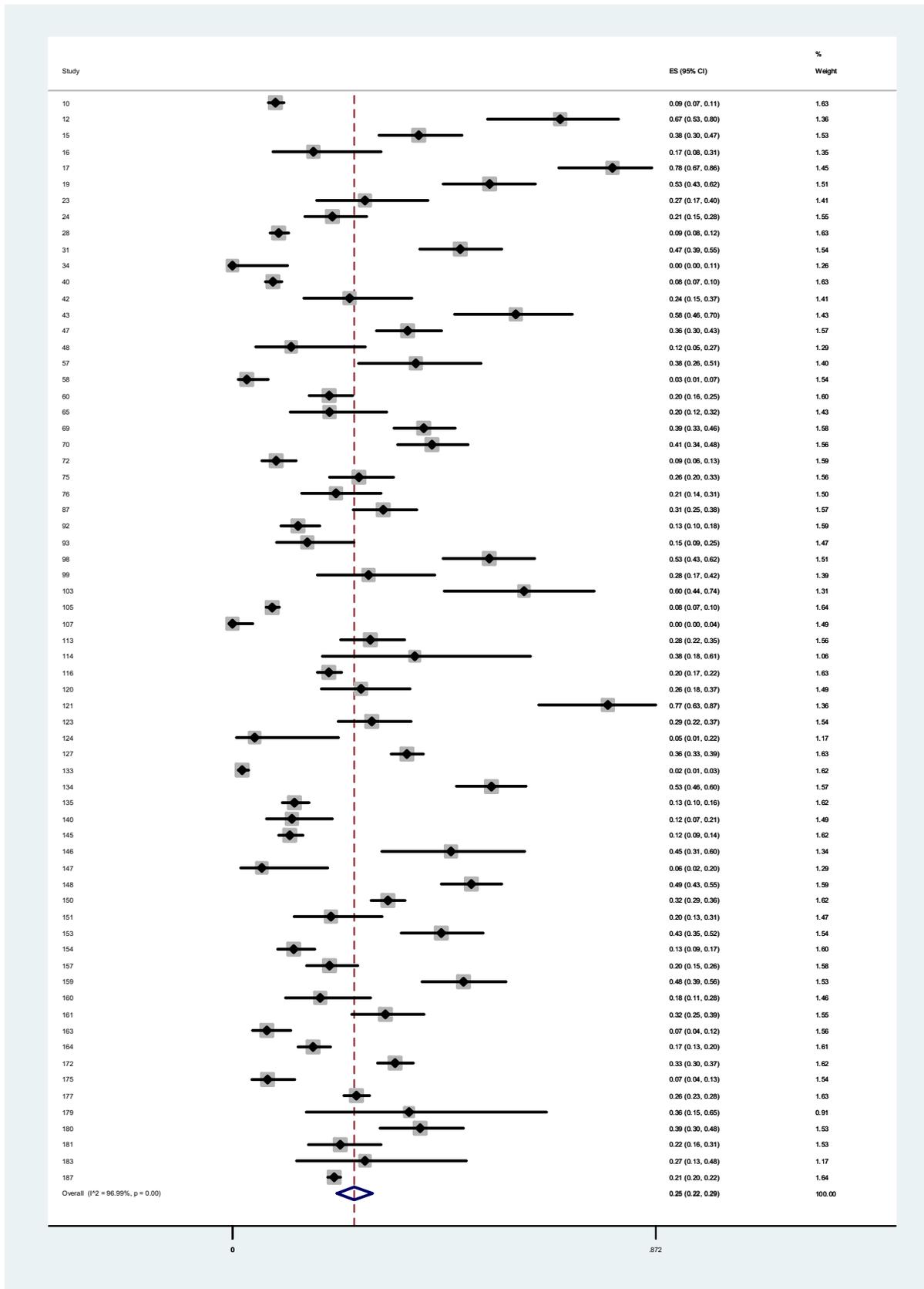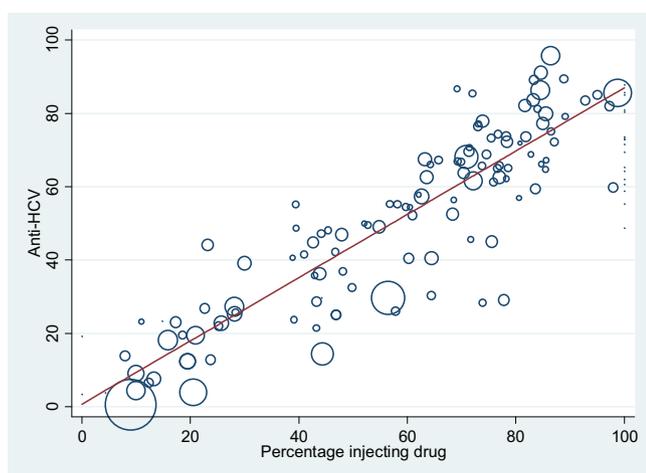
Figure 7. PWID.

Figure 8. PWUD.

Figure 9. Weighted linear regression. Meta-regression for anti-HCV prevalence among drug users by proportion of study sample reporting injecting drug use.

seroprevalence among PWID reported in this analysis compared to previous reports warrants further investigation.

Conflict of interest

There is no conflict of interest.

Funding source

Ethical approval

Ethical approval was not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2018.11.006.

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