REVIEW ARTICLE

AN UPDATE OF HEPATITIS C PREVALENCE RATES IN HOMELESS ADULTS AFTER HEPATITIS C TREATMENT PARADIGM CHANGE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: An estimated 100 million people are homeless around the world. Concurrent vulnerabilities, such as psychiatric diseases, addictions with unsafe injection practices increase blood-borne infections risks, including HCV in homeless individuals. A 2012 Lancet Infectious Diseases paper reported HCV prevalence in homeless ranging from 3·9% to 36·2%, but we know very little about HCV treatment in homeless, aside from the fact that treatment is rarely if at all provided or considered. Old treatment regimens from the "interferon era" had many psychiatric side effects, including increased suicide and major depression rates and were contraindicated in patients, who had pre-existing or secondary psychiatric diseases, addictions, and were unstable. Meanwhile, treatment

paradigm has changed in HCV management recently. Current HCV treatment options are not contraindicated in people with psychiatric conditions anymore and can help successfully achieve HCV cure. Additionally, new treatment options are shorter in duration, all-oral instead of injections with easier to adhere regimens, and are recommended by current guidelines in unstable individuals as well. This study objective is to update previous study findings, and examine HCV treatment prevalence in homeless adults.

Methods: On February 2016, we searched PubMed, EMBASE, and Cumulative Index to Nursing and Allied Health Literature databases for "homeless* and (hepatitis C or HCV)" for studies reporting HCV prevalence in homeless adults published between 31 January 2012 and 15 February 2016. Meta-analysis was conducted following the PRISMA Checklist. Data was tabulated in Comprehensive Meta-Analysis.

Findings: Fifteen epidemiological studies yielded. The omnibus prevalence rate for HCV in homeless remains unchanged since 2012, (28%; 95% CI: 23-34; N=15). Only three studies reported HCV treatment investigation, but the data quality could not allow a meta-analysis.

Interpretation: Despite a high HCV prevalence among homeless, HCV treatment prevalence information is limited; some studies mention that treatment is not practically provided. This meta-analysis data can help to estimate the frequency of HCV infection, which can help to plan HCV management services for homeless population in a better way. Together with the recent advancements, paradigm changes in HCV treatment the data from this review can also contribute to the global HCV elimination goal.

Key words: Hepatitis C, Homeless, Meta-analysis, Prevalence, Systematic Review

Introduction

Homelessness is a global issue affecting many people worldwide.[1] Estimates vary depending on homelessness definition, but social, physical, and mental health-related (primary and secondary due to illicit drug use) issues are highly prevalent in all categories of homelessness. One of the major concerns is high, but still increasing prevalence of Hepatitis C virus (HCV) infection in homeless.[2]

HCV infection is blood-borne infection, constituting a serious health issue, and, if untreated, may lead to liver cirrhosis, hepato-cellular (HCC) carcinoma, and death.[3] World Health Organization (WHO) estimated approximately 3% of world's population has been infected with HCV.[4] About half of those infected are not aware of their infection, contributing to a "silent epidemic", which constitutes a substantial burden on healthcare systems.[5] The accurate estimation of the number of HCV infected has inherent limitations and contributes to less effective HCV prevention and management.[5, 6] Homeless are among populations with a higher rate of HCV infection, in some cohort of homeless has been reported to be as high as 87·6%.[7] HCV infection is a significant predictor for hepatic fibrosis in homeless, which is associated with earlier mortality.[8]

Although HCV infection is manageable, overall treatment rates are low. Extremely low rates in homeless may be due to lack of access to healthcare services, lack of awareness, low prioritization, and concerns about psychiatric side effects from old HCV

treatment regimens added to pre-existing psychiatric and concurrent disorders. In addition, higher prevalence of intravenous drug use (IVDU) in homeless can contribute to the lower uptake of HCV treatment.[9] Above-mentioned factors make homeless ineligible candidates for HCV treatment.

The systematic overview conducted by Beijer and colleagues in 2012 estimated HCV prevalence in homeless ranging from 3·9% to 36·2%.[10] With recent paradigm changes and advancements in HCV treatment, the current clear estimates of HCV treatment rates in homeless is important. Many vulnerabilities, including high rates of psychiatric illness in homeless, precluded them from HCV treatment eligibility. Longstanding "Interferon era" treatment regimens included interferon, which is contraindicated in patients with mental illness. However, some novel HCV treatment choices do not have contraindications to patients with psychiatric co-morbidities because they do not include interferon, are shorter in duration, are once-daily oral regimens with better compliance, are easier to tolerate because of fewer side effects, and have higher rates of treatment success, sustained virologic response (SVR).[11, 12] Due to the recent paradigm shift in HCV management in homeless, it is important to assess how current treatment guidelines of targeting homeless individuals with vulnerabilities are met. Homeless people with many vulnerabilities were not traditionally offered HCV treatment, currently can be offered. Accurate estimates of HCV and its treatment prevalence will inform planning services of prevention and management of HCV infection in homeless.

The objective of this study was to determine the current HCV prevalence rate among homeless, following the same methodology as the study conducted by Beijer and colleagues in 2012 [10], examine for possible changes in the HCV prevalence rate, and examine if any of the studies reported on treatment prevalence for HCV in homeless.

Methods

We searched PubMed, EMBASE, and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for "homeless* and (hepatitis C or HCV)" published between 31 January 2012 (after systematic overview by Beijer et al, 2012) [10] and 15 February 2016. When appropriate, reference lists were searched. Additionally, researchers conducting studies on population with housing issues and HCV were contacted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report the prevalence rate. We included eight papers with the HCV prevalence from the 2012 review (four papers were excluded from 2012 review because included not adult population only and were conference proceedings or thesis). New search conducted on 15 February 2016, after deleting duplicates, revealed 156 additional papers published after the 2012 systematic overview by Beijer et al. Studies that grouped prevalence rates of homeless and non-homeless, HCV and HIV, with unclear methodology or those that reported just for people who inject drugs (PWID) and not homeless, were also excluded. After the exclusion, 43 papers remained, fulfilling inclusion and exclusion criteria. After considering papers with HCV prevalence in homeless inclusion criteria, six papers were added (included also data from one research survey from raw data [13] to the eight included papers (15 in total) (Figure 1).

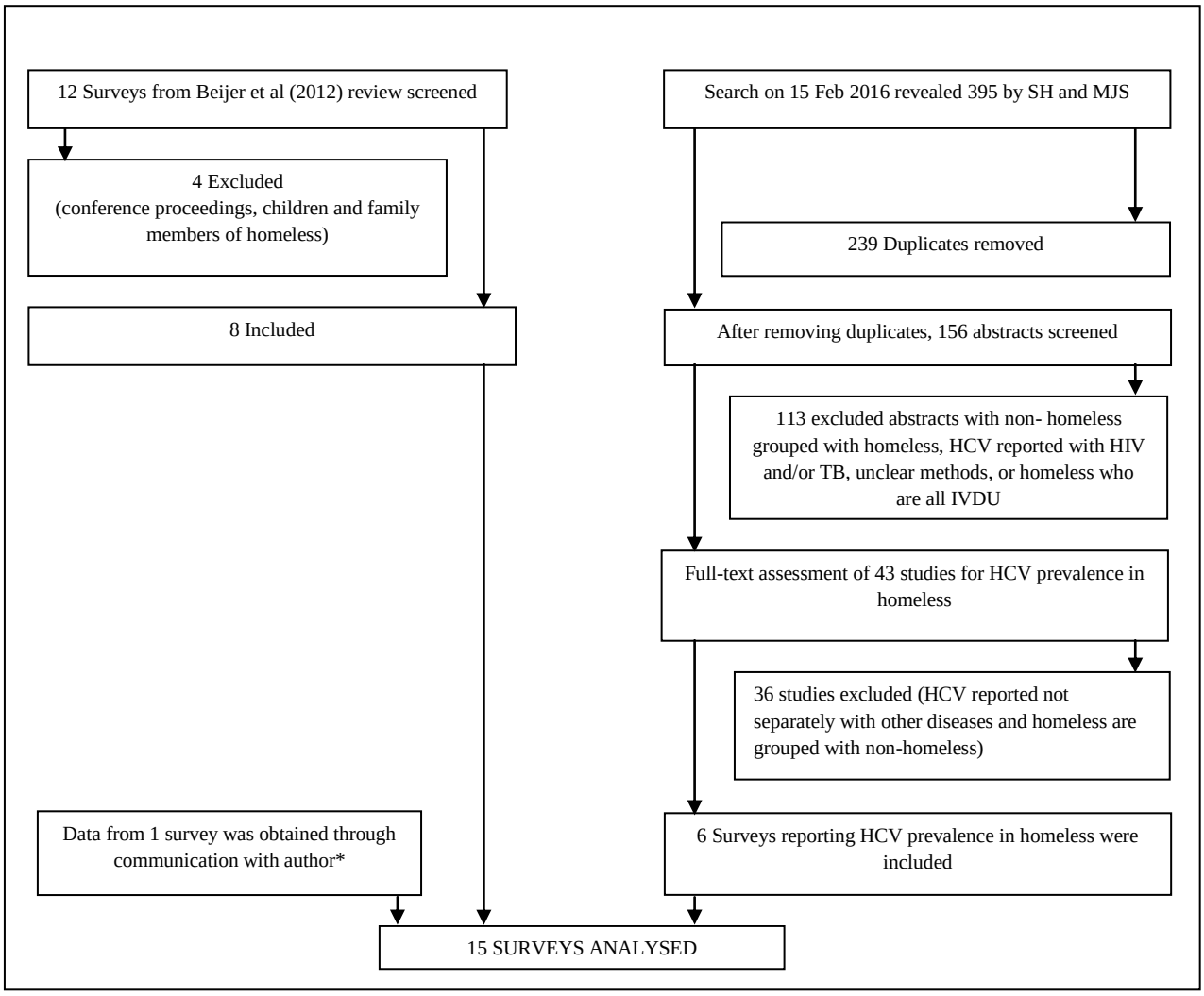

Figure 1. Flow diagram showing study selection

*Brian Conway M.D, F.R.C.P.C, conducting research in homeless population Vancouver, from raw data

Meta-analysis was performed to calculate the estimate of HCV and its treatment prevalence in homeless population.

This review included all studies published in English in which the study participants were homeless adults (with defined absolute or precarious homelessness) and who were diagnosed with the HCV infection (we also included studies that relied on self-report). The primary outcomes of interest were: HCV infection prevalence and treatment prevalence in homeless based on rapid antibody tests/HCV antigen, self-reported HCV positive/cured from questionnaires, HCV RNA/confirmatory tests, self-reported initiated/finished treatment, and administrative data. The secondary outcomes were HCV infection risk factors in homeless. All studies that reported HCV prevalence in homeless, HCV treatment in homeless, were included.

Two independent review authors (SH, MJS) examined the study titles and abstracts,

identified eligible studies based on the inclusion criteria. Decisions of two authors were recorded separately and in case of disagreement were discussed. In the absence of consensus, a decision was made by the third reviewer (AAS), and finally, by the supervisory author (MK). A full text review was performed for the above selected studies and recorded into a study selection form demonstrating the reason for exclusion/inclusion of each study.

For obtaining an omnibus prevalence rate estimate (global prevalence rate), and aggregate prevalence (AP) rates with associated 95% confidence intervals (CI), we have transformed the reported number of cases of HCV per number of homeless to a percentage. Then, the percentage with the associated sample size for each study was used in the Comprehensive Meta-Analysis (CMA) software (CMA: Version 2.0) [14] to calculate event rate estimates, assessing heterogeneity, publication bias, and graphing figures. For all analyses, the use of random effect model was set a priori, and used alpha 0·05 as a cut-off for statistical significance.

The presence of between studies heterogeneity was appraised using the Cochran's Q (reported as $\chi 2$ and p values) and its magnitude via the I-square statistic (I^2).[15, 16] For I^2, values of 25%, 50%, and 75% show low, moderate, and high degrees of heterogeneity, respectively.

For meta-regressions, appraising the effect of a priori set moderating factors, method of moment was used.[17] For assessment of publication bias, funnel plot and quantitative methods (Begg and Mazumdar correlation, and Egger's regression) were used.[18, 19] For Fail-safe N, [20] the classical method was used.

Risk of bias was categorized for included studies in the form of high, low, or unclear. Unclear was defined as either lack of information or uncertainty over the potential for bias by SH and MN. Any disagreements were addressed by discussion of SH and MN, and when necessary, resolved by AAS. Quality assessment was conducted using the validated Newcastle-Ottawa Quality Assessment Scale (NOS).[21]

Results

Our search of the literature yielded 156 abstracts for the period from January 2012 to February 2016. After duplicates removal, initial screening, and fitting for selection criteria, six studies remained.[22-27] The Lancet Infectious Diseases 2012 paper [10] provided an additional 12 studies, eight [28-35] of them were included, as they focused on homeless adults. Also, we have recurred to unpublished data from a single previously published study (Figure 1).[13]

In sum, 15 unique studies investigating the prevalence of HCV in adult homeless individuals (n=7975) constituted our sample (Table 1, Figure 2).

Table 1. Demographics of the included studies (N=15)

Study name	n	Event rate	Year	Country of data	Survey	Assertion	Average Age	Male %	Number of Shelters	Marital status	Sampling method	HCV Tx
Amiri et al	593	0·2327	2014	Iran	Yes	Ab	41	87	5	Yes	Convenience	No
Boyce et al	40	0·0750	2009	USA	Yes	Ab	39	43	1	No	Convenience	No
Brito et al	330	0·0850	2007	Brazil	Yes	Ab	40·2	81	5	Yes	Convenience	No
Conway et al	2100	0·3300	NP	Canada	Yes	Ab	42	85	8	Yes	Convenience	Yes
Gelberg et al	534	0·2670	2012	USA	Yes	Ab	45·8	74	41	No	Probability	Yes
Hermanstyne et al	1220	0·1700	2012	USA	Yes	Ab	NR	NR	39	No	Systematic	No
Nyamathi et al	884	0·2200	2002	USA	Yes	Ab	NR	NR	36	No	Convenience	No
O'Carroll et al	343	0·3615	2008	Ireland	Yes	Self-report	NR	61	22	Yes	Probability	No
Rosenblum et al	139	0·3237	2001	USA	Yes	Ab	40	68	NR	No	Convenience	No
Sherriff et al	98	0·2650	2003	UK	Yes	Ab	NR	NR	3	No	Convenience	No
Stein et al	534	0·2800	2011	USA	Yes	Ab	46	80	41	No	Probability	No
Strehlow et al	387	0·3101	2012	USA	Yes	Ab	44	73	8	No	Convenience	No
Takarar et al	278	0·3417	2015	USA	NO	Ab-EMR	49.1	77	2	No	Convenience	No
Vahdani et al	202	0·4307	2009	Iran	Yes	Ab	45	100	NR	No	Probability	No
Vila-Rodriguez et al	293	0·6792	2013	Canada	Yes	Ab	44·1	77	4	Yes	Convenience	Yes

Note: Ab: Antibody, EMR: Electronic Medical Record; NR: Not Reported. Tx: Treatment; %: percent; HCV: Hepatitis C Virus; n: number of individual enrolled in the study; NP: Not published yet.

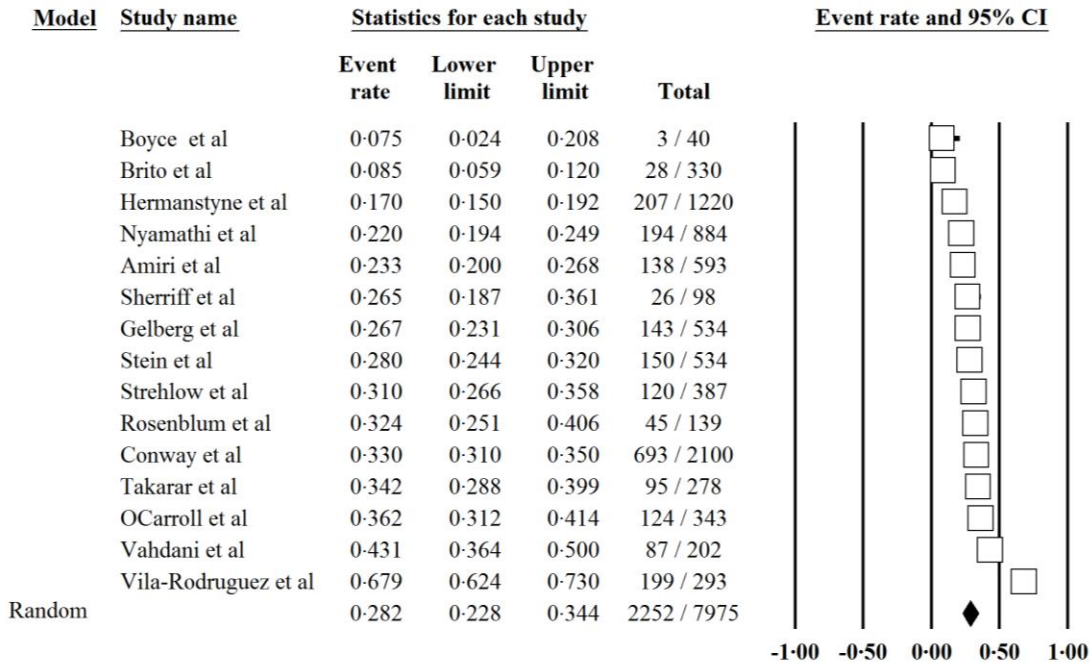

Figure 2. Forest plot showing the global prevalence aggregate for HCV in homeless people

The omnibus aggregate prevalence rate for HCV in adult homeless individuals was found to be 28% (95% CI: 23-34; N=15). Eleven of the 15 studies emerged from the American continent (AP: 27%; 95%CI: 20-34); the remaining from Asia and Europe. Fourteen of the 15 studies explicitly reported using surveys (AP: 28%; 95%CI: 22-34) and one study reported using Electronic Medical Records (EMR).

Convenience (N=10), probability (N=4), and systematic (N=1) were the sampling methods used by the included studies. Thirteen of the 15 studies reported on sample aging from 18 and over (AP 30%; 95%CI: 19-46), while two studies reported on age 15 and over. Five studies reported marital status (AP: 31%; 95%CI: 19-46), and ten did not explicitly report on marital status (AP; 27%; 95%CI: 22-33). The majority of the studies reported on homeless and impoverished individuals (AP: 27%; 95%CI: 19-36), and six studies reported explicitly on homeless individuals (AP: 33%; 95%CI: 27-38).

Fourteen of the 15 studies reported examining for physical co-morbidity (AP: 28%; 95%CI: 22-35). Six of the 15 studies reported psychiatric co-morbidities (AP: 35%; 95%CI: 24-48), while the remaining did not (AP: 24%; 95%CI: 18-31). Eleven of the 15 studies reported on incarceration (jail or prison) history (AP: 27%; 95%CI: 20-34) and the remaining did not (AP: 34%; 95%CI: 30-37).

Six of the 15 studies reported on the presence of tattoos (AP: 21%; 95%CI: 14-31), while nine did not (AP: 33%; 95%CI: 26-41).

Method for HCV diagnosis was either affirmed by self-report, EMR data, antibody testing (oral, blood), or by confirmatory RNA testing. Fourteen of the 15 studies reported using antibody testing and EMR (AP: 28 %; 95% CI: 22-34), and one study reported using self-report data. Three of the 15 studies reported on treatment for HCV (AP: 42%; 95%CI: 24-62). All studies reported examining for IVDU (Table 2).

Table 2. Estimated prevalence rates

		Effect size and 95% Confidence interval				Heterogeneity			
Random effect model		N	Point estimate	Lower limit	Upper limit	Q-value	df Q	P-value	I^2
Overall		15	28%	23%	34%	399·121	14	0·000	96·492
Without unpublished paper		14	28%	21%	35%	376·917	13	0·000	96·551
Without the smallest study		14	29%	24%	36%	391·809	13	0·000	96·682
Categorical variable									
Continent	America	11	27%	20%	34%	362·040	10	0·000	97·238
	Asia	2	32%	16%	54%	28·192	1	0·000	96·453
	Europe	2	32%	23%	42%	3·133	1	0·077	68·083
Survey	No	1	34%	29%	40%	0·000	0	1·000	0·000
	Yes	14	28%	22%	34%	395·523	13	0·000	96·713
Assertion-diagnosis	Antibody & EMR	14	28%	22%	34%	390·478	13	0·000	96·671
	Self report	1	36%	31%	41%	0·000	0	1·000	0·000
Treatment information reported	No	12	25%	20%	31%	175·199	11	0·000	93·721
	Yes	3	42%	24%	62%	139·274	2	0·000	98·564
Homeless & Shelter status	Homeless	6	33%	27%	38%	26.554	5	0·000	81·171
	Homeless/impoverished	9	27%	19%	36%	356·643	8	0·000	97·757
18+	No	2	21%	13%	31%	5·495	1	0·019	81·800
	Yes	13	30%	24%	36%	304·407	12	0·000	96·058
Marital status information reported	Yes	5	31%	19%	46%	233·463	4	0·000	98·287
	No	10	27%	22%	33%	110·603	9	0·000	91·863
Incarcerated information reported	Yes	11	27%	20%	34%	385·088	10	0·000	97·403
		Effect size and 95% Confidence interval				**Heterogeneity**			
	Random effect model	N	Point estimate	Lower limit	Upper limit	Q-value	df Q	P-value	I^2
Categorical variable									
	No	4	34%	30%	37%	3·299	3	0·348	9·063
Tattoo information reported	Yes	6	21%	14%	31%	124·934	5	0·000	95·998
	No	9	33%	26%	41%	213·990	8	0·000	96·262
Physical-Comorbidity reported	No	1	31%	27%	36%	0·000	0	1·000	0·000
	Yes	14	28%	22%	35%	398·400	13	0·000	96·737
Psychiatric-Comorbidity reported	No	9	24%	18%	31%	187·408	8	0·000	95·731
	Yes	6	35%	24%	48%	198·087	5	0·000	97·476
Sampling method	Convenience sampling	10	27%	20%	36%	280·726	9	0·000	96·794
	Probability Sampling	4	33%	26%	40%	24·398	3	0·000	87·704
	Systematic sampling	1	17%	15%	19%	0·000	0	1·000	0·000

Note: EMR: Electronic Medical Record

At the study level, single variable meta-regressions using method of moment showed a significant age effect [Slope: 0·128; SE: 0·064; P-value: 0·045; N=11], and length of homelessness [Slope: -0·032; SE: 0·010; P-value: 0·001; N=3]. At the HCV level, age [Slope: -0·213; SE: 0·051; P-value<0·001; N=3] and tattoo significantly affected the HCV prevalence [Slope: 0·055; SE: 0·009; P-value<0·001; N=5]. No effect was found for the HIV on the prevalence of HCV in homeless individuals, and no study reported examining tuberculosis in homeless individuals with HCV. The single variable meta-regression for the effect of publication

year has shown no significant effect [Slope: 0·035; SE: 0·041; P-value>0·05].

Three of the 15 studies reported on the lifetime prevalence of sexually transmitted diseases (STD) in HCV, from which, one study reported global STD to be 4·6% [35], and others reported 33·3[32] to 43·3%[36] for syphilis, 39·4% for gonorrhoea, and 28·4% for chlamydia.[36] Additionally, two studies reported on veterans, and one on baby boomers (people born during the post–World War II) (Table 3).

Table 3. Univariate meta-regressions of variables affecting the prevalence of HCV in homeless individuals

Homeless level variables	Slope	Standard error	Z-value	P-Value	N
Male (%)	1·6426	1·4077	1·1668	0·2433	12
Average Age	0·1279	0·0639	2·0030	0·0452	11
Number of shelters or clinic	-0·0059	0·0095	-0·6183	0·5364	13
Percent of the sample being homeless	1·6854	1·3673	1·2326	0·2177	15
Length of homelessness (minimum)	-0·0321	0·0100	-3·2282	0·0012	3
Number of shelters	-0·0059	0·0095	-0·6183	0·5364	13
HCV level variables					
Male (%)	-0·0004	0·0064	-0·0691	0·9449	5
Average Age	-0·2127	0·0513	-4·1494	0·0000	3
HIV	0·1471	0·2465	0·5968	0·5507	4
Tattoo	0·0546	0·0091	6·0188	0·0000	5
Incarceration/Jail/Prison	0·0054	0·0071	0·7594	0·4476	8
Study level variables					
Publication Year	0·0350	0·0411	0·8514	0·3946	14
Quality assessment	0·0229	0·0136	1·6876	0·0915	15

Note: N: Number of studies included in the analysis.

The funnel plot showed no sign of publication bias; estimated and observed values were the same. Quantitative analyses, Begg and Mazumdar correlation, and Egger's regression intercept were non-significant (P-value> 0·05); supporting the lack of publication bias. The classical fail-safe N with 15 studies in the analysis, Z-score of 1·96, alpha set at 0·05 (2-tailed), and an observed z-value of -31·575 showed that we would need over 3800 similar studies to significantly change the prevalence rate. The quality score of the studies did not seem to affect the prevalence rate for the HCV in homeless individuals [Slope: 0·023; SE: 0·0134; P-value>0·05]. The heterogeneity assessment via the Q-statistics and I^2 showed a large level of heterogeneity across analyses with the exception of reported incarceration in the homeless. The high level of heterogeneity in epidemiological studies is expected (Figure 3, 4).[37]

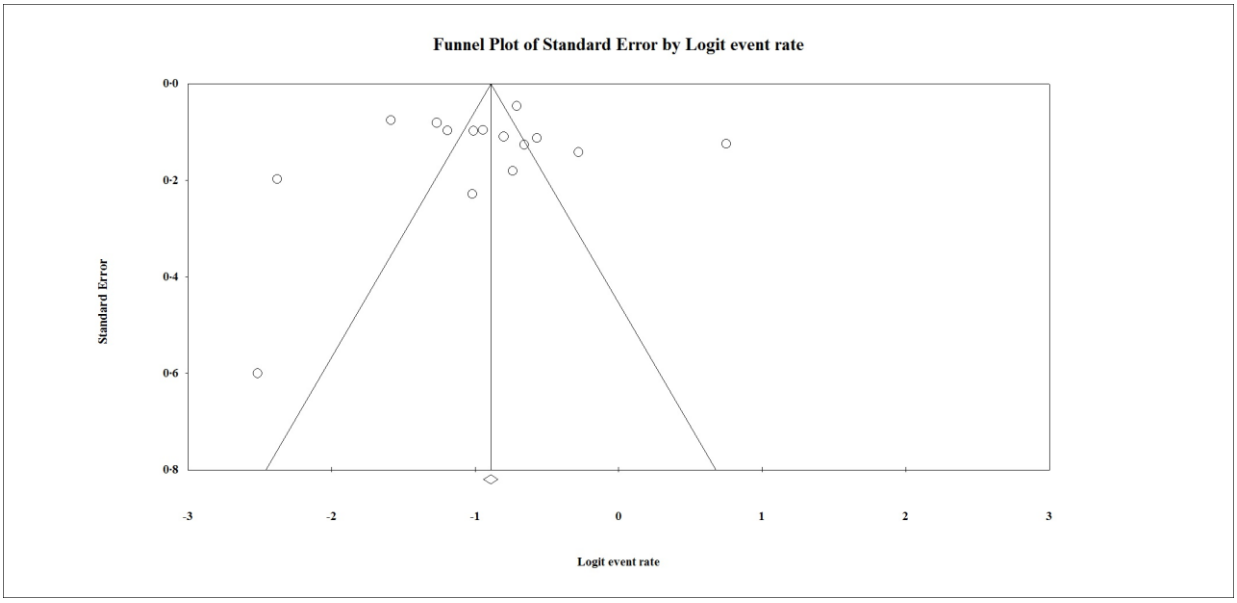

Figure 3. Funnel plot examining the publication bias

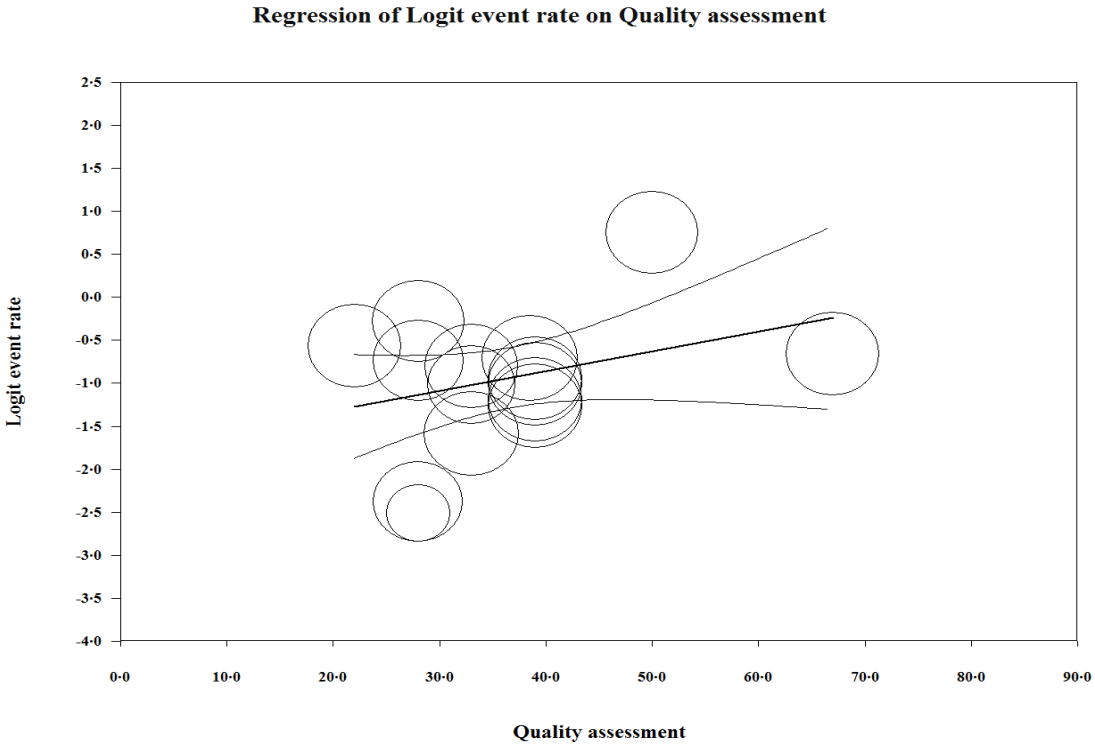

Figure 4. Quality assessment univariate meta-regression

Sensitivity analysis was conducted for the effects of unpublished data and study size with the lowest relative weight. When the only unpublished study was excluded, the AP for HCV in homeless was 28% (95%CI: 21-35; N=14) and when the smallest study with the lowest relative weight (data not shown) was excluded, the AP was 29% (95%CI: 24-36; N=14).

Discussion

Our meta-analysis, investigating the prevalence of HCV infection and treatment prevalence in homeless, included 15 studies with a total of 7975 individuals experiencing homelessness. The estimated prevalence rate was not different from the reported 2012 review: our rate was 28% (95% CI: 23%-34%) compared to the prevalence of 3·9% to 36·2% from the 2012 review. Only three of the 15 studies reported on treatment without explicit HCV treatment prevalence, which did not allow doing meta-analysis on HCV treatment prevalence. Pooled prevalence estimate of HCV among homeless in studies that reported HCV treatment was higher than pooled prevalence from the studies that did not report HCV treatment (42% vs. 25%). Due to many pre-existing and secondary psychiatric conditions and old treatment regimen issues, treatment was rarely, if at all, provided or considered. HCV treatment rate was 0% even in marginally housed population groups with the highest hazard rates of mortality being HCV associated fibrosis.[8] Conditions for treatment are changing though and more options for HCV treatment are now available.

Among studies, probable sources of bias included selection bias, convenience sampling, different definitions for homelessness, and self-reported versus seropositivity/RNA tests. Due to vulnerabilities associated with homelessness, including prevalent psychiatric different conditions and technical difficulties to collect data in these individuals, the convenience sampling was used in the majority of the studies to satisfy the requirements of the study. Only one study used EMR information to collect data, the rest used survey methods. The majority of the studies (N=10) used convenience, only four used probability, and one used the systematic sampling method. This can be explained by the inherited difficulty to collect data from homeless individuals, who are highly vulnerable, marginalized, and hard to reach. The information emerged from the study that used EMR data could be reliable, but not persistent, because it could be collected during different time periods with different methods. In addition, the homeless population who was already engaged in medical care will not be representative of homeless individuals, who were not seeking any care.

Method of HCV diagnosis was affirmed either by antibody testing, self-report, or EMR data. One potential issue with this data is associated with not reported rates of spontaneously cleared cases, as studies providing self-reported data or antibody tests without confirmatory tests, cannot provide clear estimates who need HCV management.

Another limitation of available data is that 11 studies were from North America, thus studies cannot be fully representative of other continents, as homeless in other regions of the world may present with different vulnerabilities and predicting factors. In studies conducted outside of North America, the aggregate prevalence rate was higher, 30%, which can be explained with the higher rates of iatrogenic HCV infections. The somewhat higher prevalence of 30% in older than 18 years of age compared to the younger population appears plausible, as the opportunity of longer period of life-time homelessness and

associated HCV high-risk behaviours, such as IVDU, needle sharing practices and paraphernalia can contribute to it.

Nine studies reported on homeless and impoverished individuals (studies reported additional information, such as sleep location, health and related services use), while six studies reported explicitly on homeless. The aggregate prevalence for the homeless and impoverished was 27% (95%CI: 19-36), while the prevalence for the homeless alone was 33% (95%CI: 27-38). The difference in the prevalence could be explained with relative stabilities that homeless and impoverished group could have, such as staying in temporary shelters, single room occupancies (SROs), but considering themselves as homeless in surveys. To the contrary, the other group of homeless, those without reporting sleeping locations and service use had fewer opportunities for stability and probably more opportunities for risky behaviours, such as sharing needles on the streets, without any hygiene opportunities for injecting illicit drugs.

Psychiatric co-morbidities were reported in six studies with the HCV aggregate prevalence rate of 35% (95%CI: 24-48), compared to those not examining for psychiatric co-morbidities the HCV prevalence rate of 24% (95%CI: 18-31). As both, primary and drug-induced psychiatric co-morbidities are highly prevalent among PWID, HCV prevalence rates are in expected higher ranges because of unsafe injections practices in people with psychiatric co-morbidities.

For the studies reporting incarceration (jail and prison), the known high risk factor for HCV, the HCV aggregate prevalence rate was 27%, while for those not reporting, the aggregate prevalence rate was 34%. Similarly, for the studies reporting on presence of tattoo, another HCV acquiring risk factor, the aggregate prevalence rate was at the lower rate of 21%, while for those not examining for the presence of tattoo, the HCV prevalence rate was 33%. Although incarceration history and the presence of tattoo are known risk factors of HCV infection, the HCV aggregate prevalence in studies not reporting it was higher. This could be explained due to the additional effects of accompanying multiple risk factors, inherited difficulties of data collection in population with many risk factors.

The estimates from this review are important for planning further research in prevention and treatment of HCV infection in homeless, as current guidelines recommend HCV treatment initiation in unstable patients.[11, 12] For a very long period, homeless individuals were not considered for HCV treatment mainly because of their frequent underlying psychiatric disease, IVDU, and unstable condition. Old treatment regimens from the "interferon era" were contraindicated for individuals with any psychiatric illness as they had serious psychiatric side effects, including increased depressive disorders and suicide rates. Also, treatment duration was long, reaching to one year in some cases and involving weekly injection, which was very hard to maintain in unstable patients, even if side effects were not a potential issue. As current treatment options are shorter in duration (12-24 weeks), interferon free, with better cure rates, all-oral instead of injections, easier to adhere, current guidelines recommend it in unstable individuals as well, who are injecting drugs or have some psychiatric underlying issues.[11, 12]

The numbers derived from this meta-analysis can contribute to the better planning of HCV management in homeless people, which can also contribute to the global HCV elimination goal.

Authors' contribution:

SH: Main author, protocol, search, study selection, data extraction, data interpretation, manuscript preparation and submission

AAS: Meta-Analysis, figures, data interpretation, manuscript

NN: Protocol, search, data interpretation, manuscript

DK: Protocol, data interpretation, manuscript

MN: Protocol, search, study selection, data extraction, manuscript

MJS: Search, study selection, data extraction, manuscript

MB: Hepatitis C expert, data interpretation, manuscript

MV: Hepatitis C expert, data interpretation, manuscript

CS: Vulnerable population expert, data interpretation, manuscript

MK: Vulnerable population expert, protocol, data interpretation, manuscript, supervisor

Funding: None

Conflict of Interest Statements: We declare that we do not have any conflict of interest.

References

1. Toro PA *et al*. Homelessness in Europe and the United States: A comparison of prevalence and public opinion. *Journal of Social Issues.* 2007;63:505-24.

2. Csiernik R, Forchuk C, Jensen E. Homelessness, housing, and mental health: finding truths-creating change. Toronto: *Canadian Scholars' Press;* 2011.

3. Perz JF *et al*. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *Journal of Hepatology*. 2006;45:529-38.

4. Negro F *et al*. The global health burden of hepatitis C virus infection. *Liver International.* 2011;31:1-3.

5. Sarbah SA, Younossi ZM. Hepatitis C: An update on the silent epidemic. *Journal of Clinical Gastroenterology.* 2000;30:125-43.

6. Desai S, Peltekian KM. Canadian mortality rates for liver disease: taking a closer look at ICD coding. *Canadian Journal of Public Health / Revue Canadienne de Sante'e Publique.* 2004;95:198-200.

7. Wood E *et al.* Prevalence and correlates of hepatitis C infection among users of North America's first medically supervised safer injection facility. *Public Health*. 2005;119:1111-5.

8. Jones AA *et al*. Mortality from treatable illnesses in marginally housed adults: a prospective cohort study. *BMJ open.* 2015;5:e008876.

9. Mehta SH *et al.* Limited uptake of hepatitis C treatment among injection drug users. *Journal of Community Health.* 2008;33:126-33.

10. Beijer U, Wolf A, Fazel S. Prevalence of tuberculosis, hepatitis C virus, and HIV in homeless people: a systematic review and meta-analysis. *The Lancet Infectious diseases.* 2012;12:859.

11. Chung RT *et al.* Hepatitis C guidance: AASLD-IDSA recommendations for testing,

managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62:932-54.

12. EASL recommendations on treatment of hepatitis C 2015. *Journal of Hepatology*. 2015;63: 199–236.

13. Conway B *et al*. Community-based infectious disease clinics: a tool of engagement for vulnerable populations. *Hepatitis.* 2016.

14. Borenstein M, Hedges L, Higgins J, H. R. Comprehensive meta-analysis. 2 ed. Englewood, NJ.: *Biostat;* 2005.

15. Higgins JP *et al*. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-60.

16. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine.* 2002;21:1539-58.

17. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials.* 1986;7:177-88.

18. Egger M *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-34.

19. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50:1088-101.

20. Persaud R. Misleading meta-analysis. "Fail safe N" is a useful mathematical measure of the stability of results. *BMJ*. 1996;312:125.

21. GA Wells *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. *http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp2016*

22. Amiri FB *et al*. Vulnerability of homeless people in Tehran, Iran, to HIV, tuberculosis, and viral hepatitis. *PLoS One.* 2014;9:e98742.

23. Gelberg L *et al*. Prevalence, distribution, and correlates of hepatitis C virus infection among homeless adults in Los Angeles. *Public health reports.* Washington, DC: 2012;127:407-21.

24. Hermanstyne KA *et al*. The association between use of non-injection drug implements and hepatitis C virus antibody status in homeless and marginally housed persons in San Francisco. *Journal of public health* (Oxford, England). 2012;34:330-9.

25. Strehlow AJ *et al*. Hepatitis C among clients of health care for the homeless primary care clinics. *Journal of health care for the poor and underserved.* 2012;23:811-33.

26. Thakarar K *et al*. Predictors of frequent emergency roomvisits among a homeless population. *PLoS ONE.* 2015;10.

27. Vila-Rodriguez F *et al*. The hotel study: multimorbidity in a community sample living in marginal housing. *The American journal of psychiatry.* 2013;170:1413-22.

28. Boyce DEC *et al*. Viral hepatitis in a homeless shelter in Hawai'i. *Hawaii medical journal.* 2009;68:113.

29. Brito VOC *et al*. HIV infection, hepatitis B and C and syphilis in homeless people, in the city of São Paulo, Brazil. *Revista de saúde pública.* 2007;41 Suppl 2:47.

30. Nyamathi AM *et al*. Risk factors for hepatitis C virus infection among homeless adults. *Journal of General Internal Medicine.* 2002;17:134-43.

31. O'Carroll A, O'Reilly F. Health of the homeless in Dublin: has anything changed in the context of Ireland's economic boom? *European Journal of Public Health.* 2008;18(5):448-53.

32. Rosenblum A *et al*. Hepatitis C and substance use in a sample of homeless people in New York City. *Journal of addictive diseases.* 2001;20:15.

33. Sherriff LCH, Mayon-White RT. A survey of hepatitis C prevalence amongst the homeless community of Oxford. *Journal of public health medicine.* 2003;25:358.

34. Stein JA *et al*. Impact of hepatitis B and C infection on health services utilization in homeless adults: a test of the Gelberg-Andersen Behavioral Model for Vulnerable Populations. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association.* 2012;31:20-30.

35. Vahdani P *et al*. Prevalence of HBV, HCV, HIV and syphilis among homeless subjects older than fifteen years in Tehran. *Archives of Iranian medicine.* 2009;12:483.

36. Gelberg L *et al*. Prevalence, distribution, and correlates of hepatitis C virus infection among homeless adults in Los Angeles. *Public Health Reports* (1974-). 2012;127:407-21.

37. Higgins JP. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol.* 2008;37:1158-60.

